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THE INTEGRATION AND DIFFERENTIATION OF ALLERGIC PHENOMENA

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I WISH to thank the members of the American College of Allergists for the invitation to their second annual convention. The recognition you have given my work in the fields of anaphylaxis and allergy has made me most happy, although I feel that, if deserved, it is only to a modest extent. I am especially pleased that, in these later years of my life, the generosity of the College has enabled me to visit the United States, a country toward which the hopes of all freedom-loving peoples are directed.

I am not certain that I am entitled to speak authoritatively before you. You are in possession of an enormous and constantly increasing amount of knowledge concerning allergic phenomena. My investigative work belongs to the past, and is based not so much upon my own medical experience, as upon theoretical considerations. And also, we have had no access to the American literature of the last five years, and only a few of the journals have recently been available to me. You must forgive me if I quote data not generally accepted or else denied. Within these limitations, I would like to sketch briefly, "The Integration and Differentiation of Allergic Phenomena."

In 1929, in the preface to the first issue of the *Journal of Allergy*, the editor stated that the word "allergy" lacked any generally accepted scientific meaning, but that it had been adopted chiefly by clinicians to designate specific hypersensitivities. This statement implied two important criteria, first that the reactions could be caused by specific, that is, definite, substances, and second that it possessed a pathological character, although this latter connotation is not adequately characterized

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by the term "hypersensitivity." The allergic individual does not react, in a quantative sense, more than the normal individual; he reacts differently, quite differently. He is not more sensitive but qualitatively sensitive in the true meaning of the word "allergic."

This observation and its implications incorporate the entire problem. There are indeed only two questions which require answer: Why are allergic reactions specific, and why do they manifest themselves in functional and structural damage to tissue cells?

Any certain knowledge we have regarding these problems stems directly from an analysis of experimental anaphylaxis. This is especially true of those experiments which are concerned with passive transmission of the anaphylactic state from actively sensitized to normal animals by means of serum injections. Here it is not necessary to search for the cell-damaging agent as part of the injected antigen, but rather in the reaction produced by the antigen and the antibody in the actively sensitized animal. Within these limits must lie all attempts to clarify the mechanisms of allergic phenomena.

In this regard, I must quote Coca[6,7], who, considering the sharply manifested specificity of non-reaginic food allergy, recognizes as a cause "a specific antibody-like mechanism."

It seems to me, that the present separation of anaphylaxis from the greater bulk of allergic phenomena is a disadvantage since many of the gaps which would have justified such a separation are now being bridged. In almost all forms of allergy, specificity can be taken back to previous sensitization and also passive transfer has been demonstrated not only by the Prausnitz-Kuestner technique, but also by the transfer of whole blood from allergic to normal individuals. This fundamental and suggestive work was initiated, in 1919, by Ramirez[54] and in 1941, by Loveless[42] whose systematic experiments demonstrate convincing conclusions.

Integration and differentiation, as in mathematics, are also in the biological sciences equally important operations, each supplementing the other. The investigation of all the related phenomena by either method may lead to valuable results, although neither technique gives us a basic understanding of either naturally occurring or experimentally induced phenomena. The ultimate objective may well be obtained by one approach or the other. In my opinion, one cannot, at the moment, foretell which will be more profitable.

If we view anaphylaxis as a central phenomenon about which must be grouped all forms of specific sensitivity, casually related, the significance of such relationships must be substantially limited by two lacunae in our knowledge. First, in spite of an enormous amount of work, our knowledge of the exact mechanism of the anaphylactic reaction is by no means complete. Originally, we thought that we had to have an antigen-antibody reaction presumably associated with an immune-body precipitation. But this is by no means certain. The recent work of

Kabat and Landow[24] would suggest that the anaphylactic reaction may be, as described by Friedberger, a precipitation, *in vivo,* in the zone of surplus antigen and under certain quantitative conditions, in which, *in vitro,* no such precipitation occurs, the antigen-antibody complex remaining in solution. The reason for the fact that under these circumstances the intensity of the anaphylactic reaction reaches so great a height is certainly not apparent. In the experiments with passive anaphylaxis, the free antibody and the antigen in solution react within the experimental animal. How are we to relate the reaction as seen generally or humorally with that seen locally, as in the shock that occurs in the smooth muscle of a test guinea pig?

It is true that we have learned from the Schultze-Dale[12] reaction that the uterus of the normal guinea pig can be sensitized, *in vitro,* by contact with immune serum containing antibodies. We explain this by saying that the antibody is bound by the horn of the uterus. But do we really understand what this process represents? According to the current conception, the antibodies are immune-globulins differentiated from the normal globulins of blood plasma by their affinity for an antigen, but this antigen, however, is not present in the tissues of the wall of the uterus of the normal guinea pig. In any case, there is no certainty as to whether or not the antigen-antibody reaction itself is sufficient to produce the symptoms or whether the presence of a mediator of a dynamically uniform, toxic nature is required.

It might well have been considered that a toxic factor of this type, whose action becomes apparent when the shocking dose of an antigen is injected, could be due to a rapid parenteral proteolysis of the injected material, except for the experiments of Tomscik and Kurotschkin[64], who produced such anaphylactic shock by the injection of non-protein haptens, that is, by bacterial polysaccharides. This concept may be replaced by the hypothesis that histamine may be the causative substance, but this theory cannot in its turn be considered a definite and final solution to our problem. In recent reviews, Rocha e Silva[57] and also Dragstedt have had to concede that the question regarding the relationship between the antigen-antibody reaction and the release of histamine cannot, at present, be answered. Dragstedt adds that, in view of all of the phenomena regarded as anaphylactic, it cannot be decided whether the release of histamine, or histamine-like substances, considering their life-threatening character, has little or great significance in the pathenogenesis of the symptoms observed. These reservations of Dragstedt[16,17] stem directly from the experimental data demonstrating the differences in the anaphylactic reactions seen in different species of animals, as far as the histamine content of the blood in anaphylactic shock is concerned. This histamine content, as we know, is not increased in the rabbit, in the horse, and in the calf, but rather is markedly decreased, as shown by Rose and Weil[58] and by Code and Hester.[8]

The uterus of the sensitized guinea pig reacts to contact with the antigen in the Schultze-Dale technique with a histamine-like contraction. As shown by Albert and Walzer[1] this cannot be reproduced with the uterine muscles of the *Macacus rhesus* monkey. And if the experiments of Tuft[65] are decisive it cannot be reproduced with strips taken from the uterine wall of women actively sensitized to horse serum. In any case, the behavior of the smooth muscle of the guinea pig in the Schultze-Dale reaction is not completely clear.

In Dale's experiments, in order to sensitize a normal uterus, a one to five hour infusion of the muscle tissue with antiserum is necessary. According to the experiments of Kulka[30,31] the mere dipping of the horn of the uterus into a solution of antiserum for one to five minutes is sufficient.

The fact that we can make the normal, non-sensitized uterus contract with antigen-antibody mixtures, which contain free antibodies in solution, cannot be brought into harmony with the conceptions which seemed safely established and required no modification by new hypothesis. This is also true for the theories of Dragstedt and his collaborators, when they state that antigen-antibody mixtures will release histamine from the blood cells when added to normal rabbit's blood. It is not necessary to go into further detail. The experimental analysis of anaphylaxis has failed to solve, or at the best has only insufficiently solved, a series of fundamental problems. It has actually brought up new questions which require answer. The theories derived from the studies of different species of animals reveal the lack of homogenicity of the conception of anaphylaxis. It is for this reason that we should not regard allergy in human beings as a simple, special type of anaphylaxis as far as its pathogenicity is concerned.

For studies in anaphylaxis, experimental reasons require the use of guinea pigs, since in this test animal we see anaphylaxis in a form in which the lethal bronchospastic shock is an easily observed and apparent phenomenon. One may be willing to view this form of reaction as a model of the asthmatic attack in man (Kallós and Kallós-Deffner[25]), but Walzer[70], however, denies that the smooth muscle of a bronchial tree is the seat of the immunological reaction of the allergic bronchial asthma. And Rackemann[53], who reported on a considerable number of deaths occurring in asthmatic individuals, states that in these patients death occurs by choking and not in consequence of a bronchial spasm. He observed a peculiar change in the bronchial secretions which were transformed into extraordinarilly viscous mucus, completely blocking the lumina of the smaller bronchi as mucous plugs.

Research in anaphylaxis, it seems, has only partially fulfilled our desire for understanding and, giving us no definite answers, has at best only led us to expect one. This attitude has changed greatly since the first promising communications of Richet in 1902, and has developed slowly

over a period of four decades. Since it is not the answer, the interest in anaphylaxis, intensive at the beginning of the century, has somewhat abated.

On the other hand, the differentiation of the conceptions of allergic phenomena, seen in human beings, gives momentum to studies in medicine developed first as to the morphology of the pathological picture, and secondly as to the immunological findings and their interpretations.

I would like to make clear my point of view regarding the immunological criteria of allergy. Our discussion can begin with serum sickness, since it was in this condition that, for the first time, the question regarding the nature of the antibody arose. Although serum sickness does not correspond to the typical model of the two-phasic experiments which postulate the previous action of an antigen, von Pirquet and Schick[52] were in no doubt that an antigen-antibody was present. The proof in the existence of such an antibody as the cause of serum sickness was later given by Voss[68,69], whose reults were confirmed by Karelitz[26,27,28] and his collaborators.

If, in man, horse serum is injected subcutaneously and eight hours later, or perhaps several days later, the serum of a convalescent serum sickness patient is injected intravenously, there will develop, within a very short period of time, a local reaction at the site of the skin injection. If there has been an interval of four days between the two injections, the patient develops a generalized rash, which seems to originate from the point of application of the horse serum, and appears in its strongest manifestation at the site of the subcutaneous injections. This, in all its details, is an effect similar to that observed by Opie and Furth[49] when their rabbits were injected first with horse serum subcutaneously and four hours later with anti-horse serum given intravenously, producing by this method both local anaphylaxis and lethal shock. Insofar as I am informed, there is no doubt that this is an inverse type of passive anaphylaxis. In other words, a passive anaphylactic experiment with change in the succession of the reaction components is easily accomplished with equally positive results in guinea pigs (Zinsser and Enders[72]). With human serum sickness actively or passively induced, one is reluctant to acknowledge such explanations since the anaphylactic antibody is allegedly a precipitin, whereas the antibody causing serum sickness is a specific immune body not easily or simply identified with the reagins of allergy. I[14,15] personally held the opinion many years ago that the anaphylactic antibody was nothing else except a precipitin, and a number of authors, especially Weil, Osborne, Wells, and others agreed with me. Today I must confess that this would hold true only if we knew that the antigen-antibody reaction, which is the basis of the anaphylactic phenomenon, occurred in the animal organism with the formation of a precipitate and that the formation of this precipitate represents a primary pathogenic factor. But we do not know

this, and, on the contrary, according to the investigations of Kabat and Landow, it is not even probable. From the experiments by Tyler[66,67] with photo-oxidized antisera, one may deduce with the author that it is not the reaction of the antibody with the antigen which is imporant, but that the precipitation itself is essential and that the results could be caused by denaturation and should be controlled by observing the behavior of precipitins freed from lipoids (Hartley[19]). Furthermore, the flocculation termed "precipitation" is also caused by antitoxic sera and by solutions of toxins. Passive anaphylactic experiments cannot be reproduced with these components.

I do not think it of fundamental importance whether the serum of a patient suffering from serum sickness flocculates with horse serum or not[9]; it is essential only that an antibody be present which, in inverse-passive transfer experiments in man, functions in exactly the same way as does the anaphylactic antibody in the analogous experiment in the rabbit.

The differences between the various antibodies of orthodox serology are also, at least partly, smoothed out by the changes in our conceptions of the nature and origin of these substances. We have little doubt that all antibodies, as they are present in the blood stream, are immune-globulins, that is, serum-globulins modified by the antigen and electrophoretically falling into the pattern of gamma-globulins. This is also true according to Newell, Sterling, and their collaborators[48] for the reagins of pollinosis. Schönheimer, Treffers, Heidelberger, and their collaborators[56,59,60] were able to demonstrate with the use of tagged amino-acids containing isotope N.15 that animals in the stage of antibody production built up their antibodies, that is, their immune-globulins, from the amino-acids in their food in the same way they build up all the proteins of the organisms and that these are decomposed in the usual way. In one special case, corroborated by experiment[61,62], it was estimated that the life duration of one antibody molecule circulating in the blood of the rabbit was four weeks.

In the case of the guinea pig, however, if it is sensitized with 0.01-0.001 c.c. of horse serum subcutaneously, it will, however, remain anaphylactic, not for weeks, but for more than one year, and in 1929, I concluded from this[13] that the production of the antibody may become independent of the stimulus by the antigen, that is, it may become autonomous. On the basis of experiments with isotope N.15 or heavy nitrogen, we may formulate that the synthesis of modified globulins, once it has started, may persist in such a way that the antibody destruction is compensated for by new antibody formation.

It is, therefore, comprehensible that the sensitization against certain foods or chemicals may remain effective for years or decades, although new contacts with the sensitizing substances are excluded. However, this behavior is not only true of anaphylaxis and of allergy; the antibodies

against measles, yellow fever, and leptospirosis, persist in the blood throughout life, not because their formation is stirred up over and over again by latent infection, but because the effect of the antigen stimulus survives the original stimulus so lastingly. Naturally enough, passively introduced antibodies are not regenerated but are destroyed. It is, therefore, the rule that immune conditions, which have been induced passively, disappear within a short period of time.

The fact that free antibodies, or globulins, which may have been synthesized in consequence of the antigen stimulus in other ways, are serum-globulins does not exclude the fact, that, although formed as a reaction of one and the same antigen, they may show differences in behavior. We must visualize the synthesis of the immune-globulin as a process reaction within the cell, variable within the boundaries of its specificity, the formation of which can be discontinued prematurely by the expulsion of the product into the blood stream. In this way, so to speak, immature antibodies may originate. The existence of such incomplete antibodies is not only comprehensible from the physiological point of view, but also their existence may be considered highly probable, as shown by the investigations of Heidelberger and Kendall[22,23], Haurowitz[20,21] and his collaborators, Pappenheimer[50] and others. In view of the problems here under discussion, the fact is especially of interest that one and the same antigen may produce antibodies which give the precipitin reaction, *in vitro,* as well as others which form only a loose reversible union with the antigen and do not cause flocculation. These are merely carried along when precipitins of the first type are present and are also reacting.

In order to explain the results found in treating patients with hay fever by injections of pollen antigens, Cooke[10,11] assumed that in addition to the sensitizing reagin a second neutralizing antibody was formed. It was, of course, Loveless[40,41,43,44] who studied, in detail, the properties and therapeutic significance of this type of antibody.

This duplicity of antigen effect as seen with pollen extracts is quite compatible with the newer conceptions of the nature and origin of the antibodies. We need not return to the rigid conception of fixed type of antibodies.

Of course, it is impossible to maintain, for the present, that reagins are incomplete or imperfect antibodies. There are, however, certain similarities which make investigations in this direction hopeful, especially when we note that the reagins form easily reversible compounds and that it is because of this property that they are unable to neutralize the effect of the antigen upon the sensitized skin (Levine and Coca[39]). It may be that the amount of antigen and the site and method of contact all determine that, in the natural acquired sensitivity due to pollen affecting mucous membranes, only reagins are formed, but following injections of pollen extract, neutralizing antibodies occur. In this regard must

be considered the experiments of Cohen and Mosko[9] who state that guinea pigs sensitized intracardially with ovalbumin will consistently die in anaphylactic shock following a minimal shock dose, although very little precipitin can be shown in the circulating blood. Following intraperitoneal sensitization, precipitins are formed in a high titer, and the anaphylactic reactivities are relatively weaker and soon disappear.

When the skin of a normal individual is sensitized passively with a serum containing reagins, the site remains sensitive to antigen introduction over a period of several days or weeks. Since the local change in reactivity remains confined to the prepared site, it is assumed that the reagins are bound or anchored to the tissues of the skin. This bondage, however, is as little comprehensible as is the statement that other antibodies, that is, precipitins, cannot be bound.

If all antibodies are considered to be immune-globulins and the specific affinity to the antigen seems to make them differ from the normal globulins, this cannot be the cause of their anchorage to tissues which do not contain the antigen. Their greater persistence at the site of deposition, it seems, can be due only to their protein character, that is, they are acting as normal proteins should behave at this point, but also as immune-globulins. And this is indeed the case.

If one injects a human subject subcutaneously with horse serum and then after an interval of eight hours to several days injects the serum of a re-convalescent patient, a reaction will be seen only in the area of deposition of the horse serum, or at least the reaction, when it occurs, will be intensive at this site.

We have, in this phenomenon, an example of the valuable results to be gained by the close bond which at present exists between the problems of protein metabolism and antibody research. The complete utilization of this relationship, however, would only be possible if we were able to answer satisfactorily the genetic relationship between an antigen and its corresponding immune-globulin and were not forced to rely rather upon hypotheses, such as those brought forward by Breinl and Haurowitz[8], Haurowitz[20,21], Macheboeuf[45], Alexander[2], Mudd[47] and Pauling.[51] These hypotheses may appeal to us as far as their form and deductions are concerned, but they are, biologically, not fruitful, since they do not give us the answer as to how a reagin and a precipitin differ. This is the chief reason for the purely descriptive character of modern research in immunology, which is a purely phenomenologically differentiation of agglutinins, precipitins, lysins, antitoxins, or as le Dantec expressed himself sarcastically at one time, of "phenomenins."

It is, however, possible to extend the scope of our knowledge by the help of the experimental approach as shown by the work of Landsteiner[32], working with the serological and allergic reactions of simple chemical compounds. Landsteiner[35,38] showed that substances like acyl chloride or picryl chloride when injected intracutaneously into the guinea pig pro-

duced a condition which in human beings might be termed contact dermatitis. But, at the same time, the animals became sensitive anaphylactically, so that they reacted to an intravenous injection of acyl or picryl protein combinations with typical anaphylactic shock. Later, Landsteiner and Chase[37] were able to make guinea pigs anaphylactically sensitive by introperitoneal preparation with chemo-specific complex antigens derived from picryl chloride or 2,4-dinitrofluorbenzol, and were able as well to produce typical contact dermatitis. This occurred, however, only, if during the sensitization period, certain nonspecific factors were present.

Landsteiner[33] himself states that in view of these results there is no justification for defining an antigen as differing from an allergen and that it is permissible to name substances such as picryl chloride or dinitrofluorbenzol antigens because of the ease with which they lead to the production of anaphylactic antibodies.

There is another reason why we may share this point of view. Using the serum of guinea pigs sensitized by these simple substances, one may not only produce the passive anaphylactic experiment, but also sensitize the skin of a normal guinea pig by the Prausnitz-Kuestner technique.[32] This represents a further functional approximation of our concepts.

If the antibodies which sensitize the skin are identical with those concerned in anaphylaxis, we are not yet certain; but we may be sure that, although they differ in one or another manner, they stem from one single antigen, or, at least in the manifestation of their effects by means of a coupling of a homologous protein, that they both originate from a single immunological determinant of simple structure.

Furthermore, the occurrence of serum sickness and also pollenosis in animals under natural conditions is further confirmed by Landsteiner's studies, since we can produce drug allergy experimentally in animals and, therefore, cannot maintain the principle of the separation of allergy, as seen in human beings, from anaphylaxis, the only type of reaction seen in the lower animals. The sovereign position of "clinical allergy" is not endangered by this concept, since because of it we are able to observe the sick individual and recognize an allergic reaction as such, despite the external appearance of multiformity.

That our sources of knowledge are by no means exhausted may be seen in the works of Coca[6,7] on familial non-reaginic allergy, or as it was baptized with philological assistance "idioblapsie." Although through the courtesy of Dr. Coca I know of his publications, I am unable to assume any definite attitude toward this newly described form of allergic reactivity. Here the clinical re-examination of his data must have the last word.

According to the data of Coca, "idioblapsie" cannot be transmitted with the serum of the affected individual to normal individuals, or, to

put it more correctly, the passive transfer experiment by the Prausnitz-Kuestner technique is negative.

At this point, I would like to remark that all techniques of this type are primarily for the purpose of proving present, in the serum, an antibody or reagin. This is to be a substance which reacts with the antigen. We are not searching for an antibody as such, but for a specific antibody which has the property of reacting with its antigen to produce the pathological symptoms from which the donor of the serum suffers when he is affected by the antigen. We are searching for an antibody which causes hypersensitivity, or in the language of serology, for a "sensibilisin." Whether there exist, at all, antibodies which always cause this effect is very doubtful. According to present conceptions, the antigen-antibody reaction becomes pathogenic only when it occurs under very particular circumstances, under very definite but incompletely known conditions. If our understanding is correct then the experiment of transmitting an allergic reactivity may have a negative result, not because the antibody is lacking in the examined serum, but because we were unable to reproduce in the recipient just that complex of conditions necessary to produce the desired result. It may also be that the recipient is for some other reason unsuitable. Negative results, therefore, can only be used with reservations. We should remember that the Prausnitz-Kuestner experiment was, in its time, a sensational surprise, and similar surprises have since recurred several times.

For instance, in contradiction to our earlier knowledge, transfer of sensitivity from allergic humans to normal animals, as to the monkey and the guinea pig, have been made several times with certainty and unqualified success (Grove[18], Caulfield[4,5], Ratner[55], Strauss[63], Walzer[17]). Allergy of the type produced by simple chemical compounds was considered untransferrable. Landsteiner and Chase[34], however, were able to transfer such sensitivities from the serum of highly sensitized guinea pigs to those of normal animals of the same species.

Kern[29] reported that he had demonstrated a chemo-specific reagin for phthallic acid anhydride in the serum of a patient with asthma and rhinitis, the symptoms of which were produced by this substance.

It was also considered that the antibody, although not demonstrable in the serum, may still be present in the body of the allergic individual, a fact which has been demonstrated beyond all doubt, in the anaphylactic guinea pig. One assumes in these cases that the antibody is bound to the cells and the tissues. A communication of Landsteiner and Chase[34] may be interpreted in this sense, since the experimentally produced sensitivity of the guinea pig against simple chemical compounds is transmissable with exudate cells. The proofs of the existence of antibodies housed within the cells are seen in the findings of the sensitivities of fibroblasts taken from tuberculous animals and grown in tissue cultures and found sensitive to tuberculin. This sensitivity has been maintained through

several passages in culture corresponding, of course, to several cell generations (Moen and Swift).[46]

Under such circumstances, it seems to me to be permissible, when the demonstration of an antibody is not possible or not constantly possible, to take refuge in the consideration that the phenomena observed in both men and animals cannot be explained in any other way than by the supposition of a pathogenic antigen-antibody reaction.[36] This paper outlines the actual state of the field of allergic phenomena as objectively as I can describe it. If one is bound, however, by his own work, objectivity has, I believe, certain limitations. In whatever way the definite solution of this problem is discovered, I shall be happy to live to see it defined, and I hope that the scientists in this country have a share in the achievement of this goal, a share commensurable with their merits.

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BOTANICAL SURVEY OF SOUTHERN CALIFORNIA

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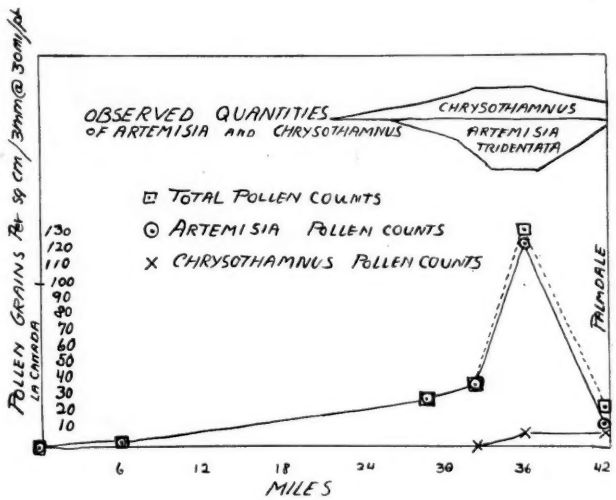
TWENTY years ago a botanical survey of allergenic plants in Southern California[6] was published in the *Bulletin of the Southern California Academy of Science.* More recently a survey of the San Diego region[8] was published in the ANNALS OF ALLERGY. Other publications[2,5,7,8] have appeared, dealing with various phases of this problem. Seven years of constant observation have convinced us that intelligent management of the allergic patient requires a more complete, and, at the same time, simplified statement of Southern California's pollen problem: completeness, so that the allergist may have, in one paper, access to all the facts, and simplicity so that the allergic-minded physician may have a guide for testing and treating many of the patients who do not need the more detailed studies of an allergist. It is no secret that Bermuda grass and ragweed account for a large number of cases of pollenosis in this region. It is equally true that many cases of what is apparently pure Bermuda grass hay fever will do better if they are given the benefit of more complete testing and antigen prescription as done by a competent allergist. There are, however, many hay fever and asthma sufferers who would be benefited by pollen treatment but fail to come to the allergist. This paper is an invitation to the interested physician to study his pollen-sensitive patients intelligently if he cannot send them to an allergist.

Most easterners and many Californians are under the impression that California pollens are of little importance. If one looks at the Durham[1] spot maps, Los Angeles looks like a haven for the ragweed sufferer, and many easterners who have had severe hay fever, and even asthma, have come to this area with complete alleviation of symptoms. Some of these people stay well; others will, after two or three years, develop symptoms again. Others come here from east of the Rocky Mountains, never having had hay fever even in that hotbed of ragweed, and develop, within months or years, severe allergic manifestations. These symptoms are frequently proved to be incited by pollen. The Los Angeles air does not ever contain great amounts of ragweed pollen. The maximum count we have ever made of downtown Pasadena air showed 20 grains per square centimeter in twenty-four hours by the gravity slide method. We have, however, made counts in a residential area only six miles from the center which ran up to 75 grains for the same slide area in twenty-four hours. This would compare in quantity with Boston, for example, where ragweed is a well recognized entity. Another factor of importance in connection with our variety of ragweed *(Ambrosia psilostachya)* is that it is a perennial, with a root system which may be 5 feet deep. Once established in a heavy

soil, which it likes, it is practically impossible to eradicate, except by planting it out with several years of grain crops. Pulling it up does little more than discourage it for a while. It is particularly prevalent in vacant



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lots in partially built-up residential areas and is increasing in quantity. Last but not least there are several close relatives of ragweed which will be discussed in more detail later in this paper.

For many years it has been stated that the pollen of a plant must have the following characteristics to be a hay fever factor: (1) wind blown, (2) of high toxicity, (3) present in sufficient quantity. I think very few allergists will argue the question of toxicity of chrysanthemum or golden rod in many persons. Neither will a competent allergist recommend banks of these flowers in the patient's room. The golden piles of pollen on the table are clear evidence of the large quantities produced and dropped by these plants. A recent trip by automobile gave a pretty clear demonstration of two facts: (1) quantity of plant as determined by observation is roughly proportioned to the actual quantity of pollen in the air during its flowering season; (2) the total quantity of pollen caught on the slide was greater from the wind blown plant *(Artemisia tridentata),* but was also present in appreciable quantity from a plant which would ordinarily be classified as an insect pollinated plant *(Chrysothamnus).* This survey was made by driving from Pasadena across the San Gabriel mountains to the Mojave Desert (black line on map). There is a very large quantity of sagebrush *(Artemisia tridentata)* just over the ridge and near the floor of the desert. In a wider area in this same location, there is a very

large quantity of chrysothamnus. There are no other compositae in any appreciable quantity in this locality. Glycerine jelly slides were exposed for three minutes outside of the car which was driven at 30 miles an hour. The curves on the accompanying chart show the pollen counts per square centimeter at various intervals along the road.

From previous experience with this method in comparison with twenty-four hour slides, it has been found that the counts are roughly comparable. The inference may therefore be drawn that there was half as much Chrysothamnus pollen in the air at this location on this day as there is ragweed at the height of the season in Pasadena, and this plant is as much insect-pollinated as is eastern goldenrod. The other point of importance is that where one observes large quantities of a known hay fever producer, there one will find large quantities of pollen during the season of pollination. We have checked this phenomenon so carefully that we feel our method of observing hay fever plants quantitatively is our most accurate guide.

In the paper by Dr. Harsh[3], he gave an ingenious method of calculating this quantitative factor. Briefly, his method was based on the quantity of pollen he obtained from cut flowering stems which were placed in water and allowed to shed their pollen over paper. In our experience this method, although highly satisfactory for collecting pollen, is likely to give an erroneous impression of quantity of pollen given off under natural conditions. We have had many experiences in collecting branches of pollinating weeds, only to find that removal from the root resulted in their failure to shed appreciable amounts of pollen, whereas another branch of the same plant, which appeared to be in the same stage of flowering, would continue to pollinate for days when not severed from the growing plant. This factor is quite variable from species to species.

The problem of specificity has been a hot point for discussion among allergists for years, and the number of papers pro and con is appalling. In general, those who have had good ground work in immunology believe firmly in the necessity of being highly specific in selecting their pollens for treatment. Among the most convincing arguments for this side of the controversy was that contained in Phillips' paper[4] on the introduction of the sugar beet seed industry in and around Phoenix, Arizona. In this paper he showed, with great clarity, that in spite of treatment with related Chenopodiaceae, sugar beet pollen was required in his antigens for certain patients. In spite of this, and a few other critical studies, many allergists—particularly those east of the Rocky Mountains—seem to get good results with timothy in their grass hay fever cases. I think, however, very few southern allergists would attempt to treat their Bermuda grass cases with timothy.

We have been impressed for many years with the similarity of skin reactions among closely related plants. For example, the vast majority

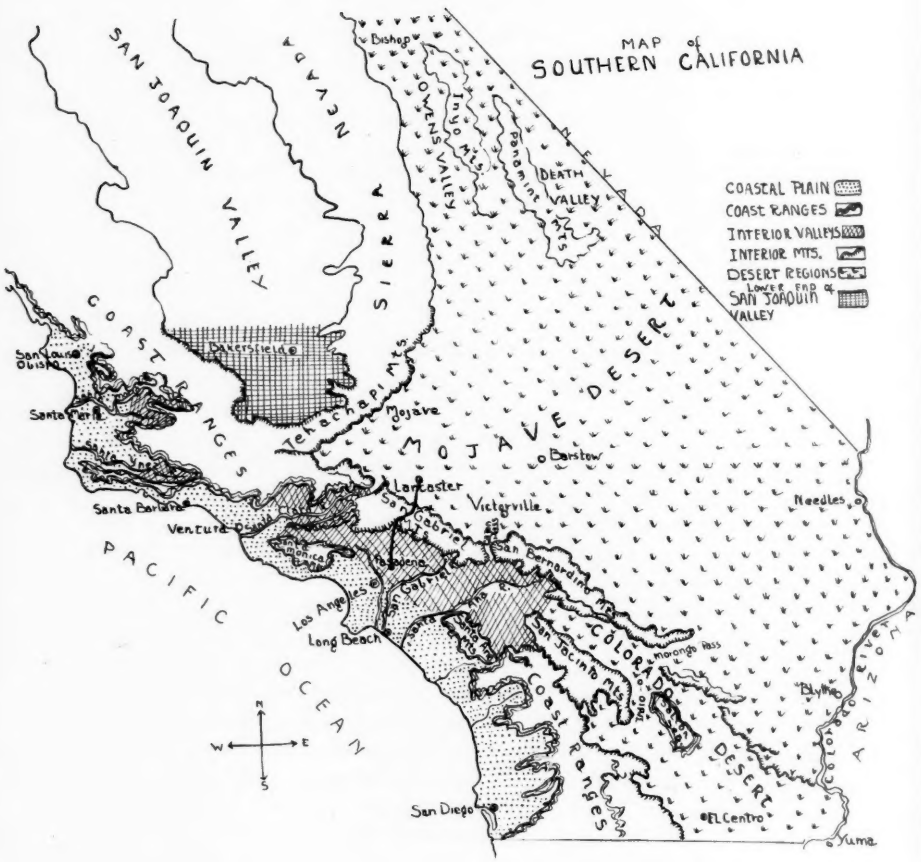
of ragweed sensitive patients show positive reactions to all of the ambrosias and franserias, particularly if great care is used in keeping the extracts used for testing of uniform strength and reasonably fresh. There is, however, an occasional patient in whom an ophthalmic test with *Ambrosia psilostachya* may be of different degree from the test with *Franseria acanthicarpa,* and the same situation occurs occasionally with the skin test. With these facts in mind, it has not seemed necessary to do the enormous number of pollen tests which have been done by some of the men in the field, but in making the antigen we are extremely careful in our selections. For example, a patient who has symptoms in the fall, lives in the Pasadena area, is found sensitive to ragweed and *Franseria,* is treated specifically with *Ambrosia psilostachya* and *Franseria acanthicarpa.* If, however, he happens to spend his winters in Palm Springs, and has difficulty in February and March there, *Franseria dumosa* and probably *Hymenoclea salsola* are added. Sensitivities to these pollens would, of course, be determined in his case. These two latter pollens would be disregarded in the ragweed-sensitive person who lives near the beach and has trouble in April or May. In this case, *Franseria bipinnatifida* would be added.

The traveling salesman may need very careful study—history being of vital importance, according to regions visited. The map will aid in understanding these regions better.

Although the botany of southern California is a very complex affair, we have attempted to simplify and clarify the problem: (1) by listing on a geographical basis, and (2) by using three kinds of type in the lists. The capital-lettered listings are, in our opinion, the most wide-spread and most frequent offenders. With careful history and testing one will find some patients who will have clinical symptoms from certain of the black type pollens. The light type attempts to list most of the other possible offenders. A supplementary list is added at the end of the regional lists. These are plants that should be known and could be considered in certain cases, such as in farmers, inhabitants of brushy hills, or children who play in fields. Included are: (a) anemophilous plants (wind-pollinated) of low antigenicity; (b) entomophilous plants (insect-pollinated) occurring in large quantities, forming the main covering in certain areas, some producing great amounts of pollen after the rains are over; (c) occasional anemophilous plants of known antigenicity (ornamental or native).

An occasional person may have some ornamental tree or shrub in his yard which is his primary cause of trouble. A home visit will at times solve the problem. Large flower gardens of plants containing highly toxic pollen may at times be the causative factor.

We have considered southern California to be that portion of the state lying south of a line between Morro Bay and Kingston, Nevada, latitude 35. Southern California may be divided into the following


MAP of SOUTHERN CALIFORNIA
COASTAL PLAIN
COAST RANGES
INTERIOR VALLEYS
INTERIOR MTS.
DESERT REGIONS
LOWER END of SAN JOAQUIN VALLEY
SAN JOAQUIN VALLEY
SIERRA NEVADA
COAST RANGES
MOJAVE DESERT
COLORADO DESERT
PACIFIC OCEAN
ARIZONA
Bishop
Owens Valley
Inyo Mts.
Panamint Mts.
Death Valley
Bakersfield
Tehachapi Mts.
Mojave
Barstow
San Luis Obispo
Santa Maria
Santa Barbara
Ventura
Lancaster
Victorville
Pasadena
San Gabriel Mts.
San Bernardino Mts.
Los Angeles
Long Beach
Santa Ana Mts.
San Jacinto Mts.
Morongo Pass
Needles
Blythe
Coast Ranges
San Diego
El Centro
Yuma
N
W
E
S

geographical regions: (1) *the Coast Ranges,* (2) *the Coastal Plain,* (3) *the Interior Ranges,* (4) *Interior Valleys,* (5) *the Desert Regions*—of which this survey covers two definite regions: (a) the Colorado Desert, (b) the Mojave Desert, including Owens Valley, (6) *Southern End of the San Joaquin Valley.*

A brief description of each region follows.

1. *Coast Ranges of Southern California.*—These are divided into two large masses by the Los Angeles Basin where three rivers enter the sea. The northern section is a broad mass of broken chains running parallel to the coast and at various angles to it. Included in this mass are the southern end of the Santa Lucia Mountains, the mountains of Santa Barbara and Ventura counties, the Santa Susanna Mountains and the Santa Monica Mountains. They range up to about 4,000 feet in altitude. Most of the vegetation belongs to the Upper Sonoran life zone and consists in great part of a dense covering of shrubbery known as the hard chaparral. The most common genera in this pigmy forest, or chaparral, are *Ceanothus, Adendostoma, Quercus, Cercocarpus, Arctostaphylos, Rhus* and *Rhamnus.* Most of these plants produce heavy bloom in the spring, although only *Quercus* and *Cercocarpus* are definitely wind-pollinated. In the more northerly sections *Castanopsis sempervirens* is a common wind-pollinated shrub. The pollen season of the chaparral extends from January, when *Ceanothus cuneatus and Ceanothus crassifolius* begin, until the middle of June when *Adendostoma fasciculatum* finishes. The chaparral then becomes very dry and goes into a dormant state. Oaks, sycamores, alders and cottonwoods grow in the canyons of these ranges and California black walnut *(Juglans californica)* is very common on the eastern slopes. The western slopes of the hills up to about 1,500 feet are characteristically covered with grasses, *Avena fatua* being the most common, with vast amounts of *Artemisia californica* and *Salvia* interspersed. *Artemisia californica* increases upwards from the coastal plain, meeting and blending with the chaparral belt, finally being ruled out by the dense growth of shrubs. This artemisia appears wherever there is a clearing of chaparral and again in large quantities on the lower eastern slopes, with grasses. Between the ranges of hills and mountains are pleasant grass covered valleys. Rank summer weeds grow along the streambeds, especially *Artemisia vulgaris.* The grasses of this region are spring pollinating.

South of Los Angeles the coast ranges begin with the Santa Ana Mountains and sweep out toward the sea north of San Juan Capistrano, continuing near the sea to San Diego, though indented by numerous valleys. These mountains include the Laguna Mountains, the Cuyamaca Mountains and all the mountains of San Diego County except the Santa Rosas and the mountains bounding the desert. These innumerable rugged chains compose a thick mountain mass, somewhat higher in elevation

than the northern coast ranges. It becomes ever more arid to the east, ending in true desert mountains.

The chaparral belt of the southern coast ranges is similar to that of the northern section, although somewhat less luxurious in growth and containing more *Adenodostoma*. The valleys and seaward slopes are grassy and there are great quantities of *Artemisia californica* all through the ranges and valleys, the chaparral being less dense. On some of the higher ridges there is timber of oak and evergreen trees, while sycamore, oaks and cottonwoods thrive in all the canyons.

2. *The Coastal Plain.*—Three practically parallel belts characterize this section.

(a) The beaches have a sparse zerophytic flora. Here *Franseria bipinnatifida,* forming mats upon the dunes, is of allergenic importance.

(b) Between the beach and the plain, there is a band of halophytes, plants adapted to excess mineral soil content (salt, alkali). The many species of *Atriplex* are charactertistic and abundant members of this band. Where the hills recede at drainage basins, these halophytic plants spread out into marshes and wastelands, sometimes stretching for miles inland. For example, *Atriplex breweri* follows the Santa Clara River inland as far as Castaic and beyond, over forty miles. The southwesterly section of the Los Angeles Basin, where the Los Angeles River and the San Gabriel River approach the sea, is a broad area over ten miles square of marshes and waste flats, covered with various members of the Chenopodiaceae. This land, however, is being gradually converted into agricultural fields and industrial or residential sections, thereby changing the atmospheric pollen content.

(c) The plain itself is a fertile band of soil originally grass-covered, that stretches along the coast to the base of the hills. At times narrow, it widens into large areas where the hills recede. These latter areas are cultivated, yielding many rich crops, and sustain large populations. The coastal towns are situated on this plain, hence we find in this section grass lands and cultivated lands with crops and ornamental plants.

3. *Interior Ranges.*—These mountains are: (a) the Tehachapi Mountains, which may be visualized as a continuation of the Sierra Nevada, swinging south and west to join the coast ranges, bounding the lower end of the San Joaquin Valley on the south and the Mojave Desert on the north; (b) the San Gabriel Mountains; (c) the San Bernardino Mountains; (d) The San Jacinto Mountains which pass southward into the rugged ranges of the Santa Rosas. These interior mountains are covered for the most part, as are the coast ranges, with solid hard chaparral but in their higher altitudes, from about 5,000 feet, the flora of the Transition Zone flourishes, with timber of pine and deciduous oak.

The important allergenic plant *Artemisia tridentata* or Mountain Sage

Brush grows in quantities on the northern and eastern slopes of the San Gabriel and San Bernardino Mountains, forming a band between the desert growth and the chaparral, growing at increasing altitudes going south, and filling large valleys and plateaus in the San Bernardinos. It also grows in abundance on the eastern slopes of the Santa Rosa Mountains. The dates of pollination of this plant vary strictly according to altitude. It starts to bloom the 15th of August at 7,000 feet, and not until the last of October or even later at 2,000 feet.

There are a few shrubs in the chaparral of allergenic importance, not necessarily typically wind-pollinated plants, but because of the great masses of flower and the extreme dryness of the atmosphere this pollen at times becomes a factor. The fact that both children and adults spend vacation time in the mountains gives these plants importance.

On the foothills we find again, as in the coast ranges, quantities of *Artemisia californica*. The pollinating habits of this plant are interesting and worth noting. Along the coast where the air contains more moisture and the plants are washed by summer fogs, the coastal sage has a regular pollination season, July and August. On the hills surrounding the interior valleys and on the foothills of the inland ranges its habits of pollination are variable, due to increased aridity and dryness of the air. It is dormant in the summer, withered in appearance. It begins to form buds, however, in late September. After the first good autumn rain these grow, and almost exactly eighteen days after the rain these buds burst into bloom, the pollen being all dissipated in about one week. Some years when there are light rains in the fall some bushes, apparently those receiving enough moisture, will bloom while others will await heavier rains. In 1939, the majority of these plants pollinated for two weeks in the middle of January after a dry fall and heavy rains the first of January. This is an example of adaptation to semi-desert conditions.

4. *Interior Valleys.*—These valleys are: (a) the Los Angeles Basin, composed of the San Gabriel Valley and the San Fernando Valley; (b) the San Bernardino Valley crossed by the Santa Ana River, and the Santa Ana River Valley in Orange County; (c) the Santa Clara River Valley in Ventura and Los Angeles Counties; (d) the Santa Inez River Valley, the Santa Ana River Valley and other smaller valleys drained by rivers rising in the coast and interior ranges. These valleys stretch inland along rivers or lie between the coast and inland ranges. They are all rich, irrigated and cultivated to concentrated groves and field crops. Here is the best home for *Ambrosia psilostachya* and *Sorghum halepense*, both of which grow abundantly with other rank weeds in ditches, stream beds and around irrigated and fallow fields. The beds of all these rivers are wondrous weed gardens, all the summer and fall wind-pollinated weeds growing togther in luxurious profusion. In these same river beds cottonwoods and sycamores rain pollen in the spring.

5. *Desert Regions.*—This vast region comprises all of California, lying east and south of the Sierra Nevada, east of the Tehachapi, north of the San Gabriel, northeast and south of the San Bernardino, east and south of the San Jacinto and east of the Santa Rosa Mountains and the mountains of San Diego county, and stretching to the Colorado River. Although the two deserts fuse and authorities differ as to boundaries, we consider in this paper the boundary between the Mojave and the Colorado Deserts to be approximately a line extending from Morongo Pass eastward to Riverside Mountain on the Colorado River.

(a) The *Colorado Desert* lies at a low altitude, mainly from 100 feet below to 1,500 feet above sea level. Palm Springs and other winter resorts are situated in the Coachella Valley in the northeastern end of the desert. *Hymenoclea salsola* is plentiful in this region, and it puts out prodigious amounts of pollen which looks similar and is antigenically closely related to the ragweeds. It blooms in February and March. *Franseria dumosa* is also abundant here and begins to pollinate in March, so that there is a long season for the *Ambrosiae* (ragweed tribe). *Dicoria,* another relative of ragweed, is also here in quantity. Farther south, in the Imperial Valley, there is a large permanent population. Irrigated fields account for rank growths of weeds, particularly *Atriplex,* and grasses. Bermuda grass is abundant and blooms practically the year round. Species of Chenopodiaceae abound from north of the Salton Sea to the Mexican border, there being an impenetrable jungle of *Atriplex lentiformis* spreading for miles around the shores of the Salton Sea, and acres covered by solid masses of other species.

(b) The *Mojave Desert* lies at a higher level than the Colorado Desert, the altitude ranging from 2,000 to 5,000 feet above sea level. The rainfall is usually somewhat greater, the winters colder. Here again we find *Artemisia tridentata.* Although this plant occurs on the desert slopes of the San Jacinto and the Santa Rosa Mountains, it is much more extensive in range and quantity in the Mojave Desert, occupying large tracts on the eastern slopes of the Sierra Nevada Mountains and the Tehachapi Mountains, on the western mountain boundaries, and in the northern part of this desert, passing on to cover large parts of Owens Valley and Mono County. At its northern end the Mojave gradually passes into the Owens Valley, of which Bishop is the principal town. This long valley is bounded by the Inyo Range on the east and the Sierra Nevada on the west. It was originally a natural sink, the old borders of the lake and the surrounding land being strongly alkaline, hence we find the Chenopodiaceae, and other halophytic plants of the Lower Sonoran life zone. This area is included in this survey because many Southern California people travel through here, spring, summer and fall, on their way to the Sierra Nevada, Lake Tahoe and Nevada.

6. *Southern End of the San Joaquin Valley.*—This section is also a sink without drainage and much of the soil is alkaline. Again we find that the

natural vegetation of the floor of the basin belongs to the Lower Sonoran life zone, with Chenopodiaceae and other plants conditioned to alkalinity growing in profusion. There are now large areas under irrigation stretching out from Bakersfield, and in these sections we find rank weeds and grasses. The hills surrounding on all sides are natural range lands, characteristically covered with indigenous grasses, and widely spaced deciduous oaks *(Quercus lobata)*.

DISCUSSION

It can be seen from the map that a person living in Pasadena would be subjected to pollens from interior valleys and coast ranges. If, however, he travels around occasionally, as we all do, he may get into any of the other divisions. Primary consideration should be given to his close environment.

If a person lives in Beverly Hills and works in Los Angeles, he is subject to pollens of the interior valleys, coast ranges and, when the wind is from the west, pollens from the coast lowlands are likely to reach him. Two or three times yearly Los Angeles is subject to the "Santana" or desert wind. This may bring him interior range pollens and even desert varieties.

Another factor to be remembered is that there is generally no rain from April to November except in the high mountains. In spite of the fact that insects collect pollen there is still much left on leaves and stems. When the dry desert winds blow we have seen varieties of pollen which we knew had been shed weeks and months previously.

Although the lists are long and complicated we have found that routine testing for residents of the Los Angeles area may safely be limited to about thirty. Checking the list will give the key to which these are. A resident of Mojave would need even fewer tests. For the past four years we have made it a rule to check all doubtful and negative pollen reactions by either the ophthalmic or intranasal method, and have been able to turn up some reactors by this method who would otherwise have been missed.

In conclusion, we think that southern California has perhaps the greatest number and widest variety of possible hay fever producing plants to be found anywhere in the United States, but we do not have tremendous quantities of pollen contaminating the air of our cities. We do, however, have much longer seasons of the ragweeds and grasses. It is our hope that this paper will make it possible for those physicians who are interested in asthmas and hay fevers to understand the problem, test with the pollens of their area, and treat with specific pollen antigens.

The botany of a growing community like the Los Angeles area is not a static thing. In the past twenty years the building program in West Los Angeles, for example, has been enormous. Very large areas of what was then full of the halophytic plants are now almost completely covered

by stores and residences, so much so that some of the species reported twenty years ago have almost disappeared in this area.

Lists of Allergenic Plants Divided into Geographical Areas

I COAST RANGES

WEEDS

Compositae		
ARTEMISIA CALIFORNICA	Coast Sage Brush	September
AMBROSIA PSILOSTACHYA	Western Ragweed	July 15-Sept.
ARTEMISIA VULGARIS HETEROPHYLLA	California Mugwort	July-Aug.
Franseria acanthicarpa	False Ragweed	June-July
Xanthium canadense	Cocklebur	Summer
ARTEMISIA TRIDENTATA	Mountain Sage Brush	Sept.-Nov.

Artemisia tridentata is not a plant of the Coast Ranges, but rather is characteristic of higher altitudes in the Great Basin. However, it occurs in the mountains of San Diego County. Beginning at a line running through Campo, Pine Valley and Cuyamaca north, it spreads east toward the desert as far as Imperial County, appearing in great abundance in flats and valleys in these arid mountains. It also occurs in the east slopes of the Santa Rosa Mountains of Riverside and San Diego Counties.

Chenopodiaceae		
Chenopodium album	Lamb's Quarters	May-Sept.
Chenopodium ambrosioides	Mexican Tea	Summer
Amaranthaceae		
Amaranthus retroflexus	Pig Weed	Spring-Summer
Amaranthus graesizans	Tumble Weed	Spring-Summer

GRASSES

CYNODON DACTYLON	Bermuda Grass	Feb.-Nov.
Avena fatua	Wild Oats	Feb.-May
Poa annua	Annual Blue Grass	Spring-Summer
Bromus species	Brome Grasses	Mar. 15-May 15
B. mollis	Soft Chess	
B. rigidus	Ripgut Grass	
B. molliformis		
B. rubens	Red Brome	
B. carinatus	California Brome	
B. racemosus		
Elymus condensatus	Giant Rye Grass	May 20-July
Elymus glaucus	Blue Rye Grass	April 15-June
Festuca myuros	Fescue	March-April
Festuca megalura	Fescue	March-April
Hordeum murinum	Fox-tail	March-April
Poa pratensis	Kentucky Blue Grass (Lawns and escapes)	
Stipa pulchra	Needlegrass	April-May
Stipa lepida	Needlegrass	April-May

SHRUBS AND TREES

A. Native Shrubs and Trees		
QUERCUS AGRIFOLIA	Coast Live Oak	March-April
PLATANUS RACEMOSA	Sycamore	March-April
JUGLANS CALIFORNICA	So. Calif. Black Walnut	Feb. 15-May
Quercus dumosa	Scrub Oak	March-April
Populus fremontii	Cottonwood	March-April
Salix lasiolepis	Arroyo Willow	Feb.-March
Ceanothus spinosus	Red Heart	April-May
Ceanothus macrocarpus	Wild Lilac	April-May

The following species of Ceanothus are also common in the coast ranges: C.

crassifolius, C. cuneatus (inner ranges), C. divaricatus (drier ranges), C. verrucosus (San Diego County). Ceanothus comprises the principal component of the chaparral. The bloom is heavy and the pollen though not strictly wind-pollinated is prolific, and continues from January 1 through May, as the different species pollinate successively.

Garrya veatchii	Silk tassel	March-April
Garrya fremontii	Silk tassel	March-April
Castanopsis sempervirens	Chinquapin	June-July

B. Ornamental and Crop Trees. (Planted around settlements).

OLEA EUROPAEA	Olive	May 25-June
JUGLANS REGIA	English Walnut	April
Ligustrum japonicum	Privet	May
Acacia species		January-June

Acacia floribunda flowers throughout the year. For list of species see Interior Valleys list.

II COASTAL PLAIN

WEEDS

Chenopodiaceae

ATRIPLEX LENTIFORMIS BREWERI	Lenscale	June-August
ATRIPLEX SPECIES:		
A. bracteosa	Bractscale	June-August
A. hastata	Spearscale	June-Sept.
A. rosea		
A. argentea-expansa	Silverscale	June-July
A. decumbens		
Chenopodium album	Lamb's Quarters	May-Sept.
Salsola kali	Russian Thistle	June-August
Beta vulgaris	Sugar Beet	April-June
Suaeda californica	Sea-blite	May-August
Salicornia ambigua	Samphire	June-Sept.
Chenopodium ambrosioides	Mexican Tea	June-Sept.

Compositae

ARTEMISIA CALIFORNICA	Coast Sage Brush	September
AMBROSIA PSILOSTACHYA	Western Ragweed	July 15-Sept.
ARTEMISIA VULGARIS HETEROPHYLLA	Calif. Mugwort	July-August
Franseria bipinnatifida	Sand Bur	April-Sept.
Franseria acanthicarpa	False Ragweed	July-Sept.
Artemisia dracunculus		Summer
Hymenoclea monogyra		Spring

(San Diego County and Lower California only.)

GRASSES

Graminae

CYNODON DACTYLON	Bermuda Grass	Jan.-Nov.
DISTICHLIS SPICATA	Salt Grass	Spring-Summer
SORGHUM HALEPENSIS (Holcus halepensis)	Johnson's Grass	Summer
LOLIUM MULTIFLORUM	Italian Rye Grass	May-June
Avena fatua	Wild Oats	Feb.-May
Elymus triticoides	Wild Rye Grass	May-July
Elymus condensatus	Giant Rye Grass	May-July
Bromus—5 species	Brome Grass	
See list under Coast Ranges		
Hordeum murinum	Foxtail	March-April
Hordeum nodosum	Mouse-tail	March-April
Phalaris minor	Canary Grass	April-May
Phalaris paradoxa	Canary Grass	April-May
Phalaris canariensis	Canary Grass	April-May
Polypogon monspeliensis	Bear Grass	April-May

TREES

JUGLANS REGIA	English Walnut	April
QUERCUS AGRIFOLIA	Coast Live Oak	March-April

PLATANUS RACEMOSA	Sycamore	March-April
OLEA EUROPAEA	Olive	May 25-June
Ligustrum japonicum	Privet	May
Acacia species	Acacia	Jan.-May
Salix lasiolepis	Arroyo Willow	Feb.-March
Ulmus parvifolia	Evergreen Elm	Oct.-Nov.

III INTERIOR RANGES

WEEDS

Compositae

ARTEMISIA CALIFORNICA	Coast Sage Brush	After all rains
ARTEMISIA TRIDENTATA	Mountain Sage Brush	Sept.-Nov.
Artemisia vulgaris heterophylla	Calif. Mugwort	July-Aug.
Chrysothamnus nauseosus	Golden Bush, Rabbit Bush	Sept.-Oct.
Artemisia vulgaris varieties	Mugwort	July-Aug.
Artemisia dracunculus		Summer

Other Families

Salsola kali (occasional)	Russian Thistle	April-Sept.
Plantago lanceolata (occasional)	Plaintain	Spring

GRASSES

Graminae

Bromus tectorum	Downy Chess	Spring
Bromus rubens	Red Brome	Late Spring
Elymus condensatus	Giant Rye Grass	May-June
Elymus triticoides	Wild Rye Grass	May-June
Hordeum nodosum	Mouse-tail	June
Poa secunda	Sandberg Blue Grass	Early Summer
Agrostis lepida		Early Summer
Muhlenbergia rigens	Deer Grass	Summer
Stipa pulchra	Needlegrass	May-June
Stipa coronata	Giant Stipa	May-June

TREES AND SHRUBS

QUERCUS CHRYSOLEPIS	Canyon Oak	April
QUERCUS DUMOSA	Scrub Oak	April
QUERCUS KELLOGGII	Black Oak	June

This oak is prolific in the higher parts of the San Bernardino and San Jacinto Mountains, foresting large stretches. It also grows in the higher sections of the San Diego Mountains.

Quercus agrifolia	Coast Live Oak	March-April
Ceanothus cuneatus	Buck Brush	Jan.-Feb.
Ceanothus divaricatus	Deer Brush	March-April
Ceanothus greggii and other species		Spring
Plantanus racemosa	Sycamore	March-April
Populus fremontii	Cottonwood	March-April
Juglans californica	So. Calif. Black Walnut	April-May
Alnus rhombifolia	Alder	Jan.-Feb.
Salix species	Willow	Feb.-March
Castanopsis sempervirens	Chinquapin	June-July
Garrya veatchii (not abundant)	Silk tassel	March-April

The **Tehachapi Mountains,** being more arid, differ in some respects from the rest of the interior mountains. The weeds, grasses and chaparral are similar, with the addition of some Atriplex canescens and A. lentiformis. Artemisia tridentata is found in quantities in the high central valleys and on the slopes toward the desert. The spring grasses are like the grasses of the Coast Ranges, including the Brome grasses, Avena fatua, Elymus condensatus. Elymus triticoides fills the mountain meadows. On the ridges grow Quercus douglasii (Blue Oak) taking the place of Quercus kelloggii, while Quercus lobata grows in the valleys. Quercus agrifolia, Q. chrysolepis grow on the slopes. Pinus cembroides monophylla (One-leaf Pinon) and Pinus sabiniana (Digger Pine) take the place of the Yellow and Sugar Pines of the other interior mountains.

IV INTERIOR VALLEYS

WEEDS

Compositae

AMBROSIA PSILOSTACHYA	Western Ragweed	July 15-Oct.
FRANSERIA ACANTHICARPA	Western False Ragweed	Aug.-Oct.
ARTEMISIA CALIFORNICA	Coast Sage Brush	Sept.-Jan.
ARTEMISIA VULGARIS heterophylla	Calif. Mugwort	July 15-Aug.
Helianthus annuus	Sun Flower	Spring, Summ., Fall
Artemisia dracunculus		Summer
Franseria tenuifolia	Slender False Ragweed	Aug.-Sept.
Chrysothamnus nauseosus varieties	Golden Bush, Rabbit Bush	Aug.-Oct.
Chrysothamnus viscidiflorus	Golden Bush	Aug.-Sept.
Xanthium canadense	Cocklebur	Spring-Summer
Xanthium spinosum	Spiny Clotbur	Spring-Summer

(Very localized, in neglected fields).

Chenopodiaceae

SALSOLA KALI	Russian Thistle	April-Nov.
CHENOPODIUM ALBUM	Lamb's Quarters	Spring-Summer
Chenopodium murale	Nettle-leaf Goosefoot	Spring-Summer
Chenopodium ambrosioides	Mexican Tea	Spring-Summer

Amaranthaceae

Amaranthus retroflexus	Rough Pigweed	Spring-Summer
Amaranthus graesizans	Tumbleweed	Spring-Summer
Amaranthus palmeri	Careless Weed	May-July

(San Bernardino County, and west through Arizona).

GRASSES

Graminae

A. Spring Grasses (Mostly native and annual).

CYNODON DACTYLON	Bermuda (Perennial)	Jan.-Nov.
POA ANNUA	Annual Blue Grass	March-June
Avena fatua	Wild Oats	Feb.-April
Bromus species	Brome Grass	
B. mollis	Soft Chess	
B. rigidus	Ripgut Grass	
B. molliformis		
B. rubens	Red Brome	
B. carinatus	California Brome	
B. racemosus		
Festuca myuros	Fescue Grass	Feb.-April
Hordeum murinum	Wild Barley, Foxtail	March-April
Festuca megalura	Fescue	Feb.-April
Hordeum vulgare	Barley	March-April

B. Summer Grasses (Perennials, many introduced species).

CYNODON DACTYLON	Bermuda	Jan.-Nov.
SORGHUM HALEPENSIS	Johnson's Grass	Summer-Fall
Poa pratensis	Kentucky Blue Grass	May-June
Lolium perenne	Perennial Rye or Ray Grass	May-June
Lolium multiflorum	Italian Rye or Ray Grass	May-June
Dactylis glomerata	Orchard Grass	May-Sept.
Elymus triticoides	Wild Rye Grass	May-July
Elymus glaucus	Blue Rye Grass	May-July
Elymus condensatus	Giant Rye Grass	May-July
Agrostis palustris	Cocoos Bent Grass	May-July
Agrostis verticillata	Whorled Bent Grass	May-July
Echinocloa crus-galli	Barnyard Grass	July-Sept.
Setaria viridis	Bristle Grass	July-Sept.
Stipa pulchra	Purple Needle Grass	May-July

Stipa lepida	Needle Grass	May-July
Zea mays (Strictly localized)	Indian Corn	June-Aug.

SHRUBS AND TREES

A. Native species; canyons, washes, hills.

QUERCUS AGRIFOLIA	Coast Live Oak	Mar. 15-April
QUERCUS DUMOSA	Scrub Oak	Mar. 15-April
JUGLANS CALIFORNICA	So. Calif. Black Walnut	Feb.-May
PLATANUS RACEMOSA	Sycamore	Mar.-April
POPULUS FREMONTII	Cottonwood	Mar.-April
Ceanothus species		
C. crassifolius		Spring
C. cuneatus		Jan.-Feb.
Alnus rhombifolia	Alder	Jan.-Feb.
Salix species	Willow	Feb.-March

B. Ornamental and Crop Trees.

OLEA EUROPAEA	Olive	May 25-June
JUGLANS REGIA	English Walnut	March-April
Acacia species	Acacia	Feb.-June
A. decurrens		
A. baileyana		Jan.-Feb.
A. melanoxylon	Black Acacia (Common street tree)	
A. latifolia		
A. floribunda		
Schinus molle	Pepper Tree	Late Spr.-Summ.
Ricinus communis	Castor Bean	Early Spring
Ulmus parvifolia	Evergreen Elm	Sept.-Oct.
Rosaceae	Rose Family	May-June

A great many shrubs, native and planted, of this family, bloom all at the same time in the late spring and early summer. The following common genera are included: Rosa, Prunus, Pyracantha, Photinia, Cotoneaster.

Ligustrum japonicum	Privet	May-June

V DESERT REGIONS

Part 1. The Mojave Desert, including Antelope Valley and Owens Valley.

A. Open desert; indigenous species.

Compositae

FRANSERIA DUMOSA	Burro Bush	Feb.-April
ARTEMISIA TRIDENTATA	Mountain Sage Brush	Oct.-Nov.
HYMENOCLEA SALSOLA		Feb.-April
Dicoria brandegii		Aug.-Oct.
Chrysothamnus nauseous varieties	Rabbit Bush	Aug.-Oct.

Chenopodiaceae

ATRIPLEX POLYCARPA	Allscale	May-June
ATRIPLEX CANESCENS	Wingscale	May-June
SALSOLA KALI	Russian Thistle	Apr.-Sept.
Grayia spinosa		May-June
Atriplex argentea expansa	Silverscale	July
Atriplex lentiformis	Lenscale	June-July
Suaeda suffrutescens		May-June
Eurotia lanata		May-June
Allenrolfea occidentalis		May-June
Sarcobatus vermiculatus		May-June
Kochia americana californica		March

Graminae. Grasses

Distichilis spicata	Salt Grass	March-May
Bromus tectorum	Downy Chess	March-April

Bromus rubens	Red Brome	March-April
Hilaria rigida	Galleta Grass	Late Spring
Triodia pulchella	Frost Grass	Late Spring
Panicum urvilleanum	Desert Panic Grass	Late Spring
Stipa	Needle Grass	March-April

Other families

Ephedra nevadensis (Gnetaceae)	Ephedra	Spring
Ephedra viridis	Ephedra	Spring

B. Irrigated sections; around farms, towns, habitations.

WEEDS

SALSOLA KALI	Russian Thistle	April-Sept.
FRANSERIA ACANTHICARPA	False Western Ragweed	Aug.-Oct.
AMBROSIA PSILOSTACHYA	Western Ragweed	July-Aug.

This is not found in the southern section of Mojave Desert, nor in Antelope Valley, but it is occasional in Inyo County.

Amaranthus graesizans	Tumble Weed	Spring-Summer

GRASSES

Distichlis spicata	Salt Grass	March-May
Elymus triticoides	Wild Rye Grass	May-June
Lolium multiflorum (Inyo County)	Italian Rye Grass	Summer
Phleum pratense (Inyo County)	Timothy	Summer
Agrostis species	Bent	Spring-Summer
Elymus glaucus	Blue Wild Rye	May-June

TREES

Populus fremontii	Cottonwood	March-April
Olea europaea (Few).	Olive	May-June

Part 2. The Colorado Desert, including Coachella Valley and Imperial Valley.

A. Open desert; indigenous species.

Compositae

FRANSERIA DUMOSA		March-April
HYMENOCLEA SALSOLA		Feb.-April
ARTEMISIA TRIDENTATA	Mountain Sage Brush	Sept.-Nov.
Dicoria brandegii		Aug.-Sept.
Chrysothamnus nauseosus varieties	Rabbit Bush	Aug.-Oct.

There is less Chrysothamnus and Artemisia tridentata here than on the Mojave Desert.

Chenopodiaceae

ATRIPLEX CANESCENS	Wingscale	May-June
ATRIPLEX POLYCARPA	Allscale	May-June
ATRIPLEX LENTIFORMIS	Lenscale	May-June
Allenrolfea occidentalis		April-May
Suaeda torreyana		Spring
Kochia americana californica		March

Grasses. Graminae

Distichlis spicata	Salt Grass	March-June
Bromus rubens	Red Brome	March-April
Hilaria rigida	Galleta Grass	Spring
Triodia pulchella	Frost Grass	Spring
Stipa speciosa	Needlegrass	Spring

Other families		
Ephedra californica (Gnetaceae)		April
Croton californica (Euphorbiaceae)		March-July
Plantago insularis variations fastigiata and scariosa (Plantaginaceae)		March-May

(B) Irrigated Sections; around towns, farms, habitations.

WEEDS

AMBROSIA PSILOSTACHYA	Western Ragweed	July-Sept.
AMARANTHUS PALMERI	Careless Weed	May-July
Atriplex lentiformis	Lenscale	May-July
Atriplex canescens	Wingscale	May-June
Chenopodium album	Lamb's Quarters	Spring-Summer

GRASSES

CYNODON DACTYLON	Bermuda	Spring, Summ., Fall
Elymus triticoides	Wild Rye Grass	April-June
Lolium multiflorum	Italian Rye Grass	April-June
Hordeum vulgare	Barley	Spring
Setaria viridis	Bristle Grass	May-June
Phalaris minor	Canary Grass	April-May
Avena sativa	Oats	Feb.-March

TREES

Populus fremontii	Cottonwood	March

Note on the Colorado River Region: Thickets of Populus fremontii and Salix goodingii, both wind-pollinated, line the banks of the river in the Colorado Desert. There are also vast thickets of Baccharis sergiloides (Compositae) and Tamarix gallica. The latter blooms prolifically during a long season.

VI SOUTHERN END OF THE SAN JOAQUIN VALLEY.

WEEDS

SALSOLA KALI	Russian Thistle	April-Sept.
ATRIPLEX POLYCARPA	Allscale	Spring
Atriplex lentiformis	Lenscale	May-June
Atriplex argentea expansa	Silverscale	Spring
Atriplex bracteosa		Spring
Chenopodium murale	Nettle-leaf Goosefoot	April-Dec.
Suaeda moquini		
Ambrosia psilostachya	Western Ragweed	Aug.-Oct.
Franseria acanthicarpa	Western False Ragweed	Sept.-Oct.
Artemisia dracunculus		June-July
Artemisia vulgaris varieties	Mugwort	July-Aug.

GRASSES

CYNODON DACTYLON	Bermuda Grass	March-Nov.
SORGHUM HALEPENSIS	Johnson's Grass	June-Sept.
ELYMUS TRITICOIDES	Beardless Wild Rye Grass	May-June
Distichlis spicata	Salt Grass	Spring
Avena fatua	Wild Oats	March-April
Bromus rigidus	Ripgut	April-May
Bromus rubens	Red Brome Grass	April-May
Bromus molliformis	Soft Chess Grass	April-May
Hordeum murinum	Fox Tail	March-April
Festuca myuros	Fescue Grass	March-April
Elymus glaucus	Blue Wild Rye	May

Poa annua	Wild Annual Blue Grass	Feb.-April
Agrostis species	Bent Grass	Late Spring
Phalaris species	Canary Grass	Late Spring
Stipa species	Needlegrass	April-May

TREES

Populus fremontii	Cottonwood	March
Juglans nigra	Black Walnut	May-June
Olea europaea	Olive	May-June
Quercus lobata	Valley Oak	March
Quercus wislizenii	Interior Live Oak	March-April
Juglans californica	So. Calif. Black Walnut	April-May
Fraxinus oregona	Oregon Ash	Early Spring
Platanus racemosa	Sycamore	March-April
Salix species	Willow	Feb.-March

Complete Supplementary List

1. Anemophilous plants of unproved antigenicity

Botanical Name	Common Name	Pollinating Date	Area
Cupressus macrocarpa	Monterey Cypress	Feb.-April	I, II, IV
Cupressus guadalupensis	Guadalupe Cypress	Dec.-March	IV, V
Juniperus californica	Calif. Juniper	Dec.-Feb.	IV
Cedrus deodara	Deodar Cedar	Oct.-Dec.	IV
Sequoia sempervirens	Coast Redwood	Dec.-Feb.	IV
Pinus coulteri	Coulter Pine	May-June	III
Pinus jeffreyi	Jeffrey Pine	May-June	III
Pinus ponderosa	Western Yellow Pine	May-June	III
Pinus lambertiana	Sugar Pine	May-June	III
Pseudotsuga macrocarpa	Big-cone Spruce	May	III
Libocedrus decurrens	Incense Cedar		III, IV
Abies concolor	White fir	May-June	III
Palms Species	Palms		IV
(Several ornamental species flowering at different times throughout the year.)			
Phoenix dactylifera	Date Palm	May	V. 2
Juncus acutus	Rush	Spring	II
Typha latifolia	Cat-tail	Spring	II

2. Entomophilous and amphiphilous plants of possible antigenicity.
(Most of these occur in quantity over large areas and produce much pollen. The rest are commonly planted ornamentals and street trees.)

Eucalyptus species	Eucalyptus	March-July	II, IV
Ceratonia siliqua*	Carob	Oct.-Nov.	II, IV
Adendostoma fasciculatum*	Chamise	April-June	I, III
Cercocarpus betuloides*	Mt. Mahogany	March	I, III
Cercocarpus ledifolius*	Mt. Mahogany	March-April	III
Larrea tridentata	Creosote Bush	March-June	V
Prosopis juliflora*	Honey Mesquite	April-May	V
Prosopis pubescens*	Screwbean Mesquite	April-May	V
Tamarix gallica*	Tamarisk	March-July	V
Tamarix aphylla*	Tamarisk	April, and Aug.-Sept.	V
Robinia pseudacacia	Locust	April-May	VI
Melia azedarach	Umbrella Tree	Summer	VI, V
Grevillea robusta	Flame Tree	May-July	VI
Cinnamomum camphorae	Camphor Tree	March-April	IV
Brassica campestris and other species	Mustard	Spring	I, II, IV
Eriogonum fasciculatum	Wild Buckwheat	April-August	I, IV
Salvia apiana	White Sage	April-May	I, II, IV
Salvia mellifera	Black Sage	April-May	I, III, IV
Encelia farinosa	Encelia	April-June	V

*Amphiphilous—both insect and wind-pollinated.

3. Occasional anemophilous plants of known antigenicity.

Acer macrophyllum	Big-leaf Maple	Mar.-April	III., IV.
Acer negundo	Box Elder	Mar.-April	I., IV., VI.
Betula alba	White Birch	Mar.-April	II., IV.
Fraxinus oregona	Oregon Ash	Mar.-April	III., IV.

Botanical determination of plants in these charts is according to the following authorities:

Dr. W. L. Jepson, "Manual of Flowering Plants of California"; "Flora of California"; "Trees of California."

A. S. Hitchcock, "Manual of the Grasses of the United States," U. S. Dept. of Agriculture Publication.

Harvey M. Hall, "The Genus Haplopappus."

H. M. Hall and Frederick E. Clements, "Phylogenetic Method of Taxonomy," Carnegie Institution of Washington Publication.

The authors wish to acknowledge the indispensable assistance of Mr. Frank W. Peirson, authority on the flora of the San Gabriel Mountains, in checking our identifications.

Towns	*Regions Affecting Towns*
Bakersfield	San Joaquin Valley
Barstow	Mojave Desert
Bishop	Owens Valley, Mojave Desert
Blythe	Colorado Desert
El Centro	Colorado Desert (Imperial Valley)
Indio	Colorado Desert (Coachella Valley)
Lancaster	Mojave Desert
Long Beach	Coastal Plain
Los Angeles	Coastal Plain, Coast Ranges, Interior Valleys
Mojave	Mojave Desert
Needles	Mojave Desert
Palm Springs	Colorado Desert
Pasadena	Interior Valleys, Interior Ranges
Redlands	Interior Valleys, Interior Ranges
Santa Ana	Coastal Plain, Interior Valleys, Coast Ranges
Santa Barbara	Coastal Plain, Coast Ranges
San Bernardino	Interior Valleys, Interior Ranges
San Diego	Coastal Plain, Coast Ranges
San Luis Obispo	Coastal Plain, Coast Ranges
Santa Maria	Coastal Plain
Santa Monica	Coastal Plain, Coast Ranges
Ventura	Coastal Plain, Coast Ranges
Victorville	Mojave Desert

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IMPORTANCE OF BRONCHOSCOPY IN ASTHMA IN CHILDREN. Dighiero, J. C.: (Importancia de la broncoscopia en el asma del niño). Arch. de pediat. del Uruguay, *16*:152-159, March 1945.

The author discusses the importance of bronchoscopy in diagnosis and treatment on the basis of a study of twenty cases, sixteen of which are studied in the intervals between attacks of asthma and four during attacks.

1. Those examined between attacks comprised three groups:

In the *first* group no pathological changes were visible, the mucosa was normal, there were no appreciable secretions or alterations.

In the *second* group there was severe congestion of the tracheobronchial mucosa with hypersecretion, a condition often called "allergic mucosa." The patients with these lesions of the bronchial mucosa were also subject to vasomotor rhinitis and presented personal and familial histories of allergy pertaining to the group of atopic asthma described by Coca.

Finally, a *third* group of cases showed changes resembling chronic tracheobronchitis. The mucosa was thickened, pale, dull, covered with mucopurulent secretions. There were also bronchial changes characterized by flaccidity, loss of elasticity, and limitation of movements of expansion and retraction. This flaccid state creates a favorable condition for emphysema.

Differential diagnosis between asthma complicated by bronchial infection and chronic tracheobronchitis with attacks of asthmatic dyspnea can be made only through the clinical history and antecedents of the patient. Treatment of the bronchial infection should be an integral part of the treatment. In such cases the author has had good results from repeated bronchial aspirations, bronchoscopic instillation of sulfonamides, topical applications, et cetera and, in cases where there was no great obstruction, from pulmonary nebulization, with sulfonamides or iodized oil. In addition to these local measures he advises general treatment and anti-allergic measures in cases of specific sensitivity.

2. Only four patients were studied during attacks. One case is described in some detail: that of a fourteen year old girl who had suffered from asthma since she was four years old. In all the cases examined there was congestion and edema of the mucosa, reducing bronchial permeability. The congestion was not equal in all cases, being more accentuated in patients in whom the mucosal congestion was of an allergic nature. These lesions were accompanied by thick, viscous secretions, mucous or mucopurulent. There were also changes in the tracheobronchial movements, varying with the degree of dyspnea and the tonicity of the bronchial walls. Bronchoscopically, bronchial spasm was not seen, although it has been noted by others. The changes that were actually observed were sufficient to explain the dyspnea and the difficulty of breathing characteristic of asthmatics.

When congestive lesions of the mucosa, as seen in allergic asthma, prevail the attacks start suddenly and rapidly become intense, but they yield readily to adrenalin. On the other hand, when there is bronchial infection and changes in the tone and elasticity of the bronchi, the attacks are milder but much more prolonged; they respond very little if at all to adrenalin, and between attacks the patient is subject to wheezing, especially at night and finally a permanent form of asthmatic breathing.

Bronchial aspiration, combined with bronchial insufflation of oxygen, is an emergency treatment in all cases of serious asthmatic attacks with asphyxia and cyanosis, in which other treatment has failed.

J. G.

CHROMIDROSIS ASSOCIATED WITH RAGWEED HYPOSENSITIZATION

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CHROMIDROSIS is a rare disorder of unknown cause characterized by the excretion of colored sweat. The perspiration may be tinged yellow, red, green, blue, or black, and may appear in this form; or it may develop color by oxidation in the air; or it may unite with substances on the surface of the skin to produce the abnormal color.[3] The most common forms are cyanidrosis and melanidrosis, terms indicating blue and black sweating, respectively. The bluish color is thought to be due to the excretion of indoxyl or one of its derivatives which is oxidized to indigo. The indoxyl derivative originates in the intestinal tract. Colored sweat, in some instances, has been due to the ingestion, or absorption by contact, or inhalation of certain substances such as potassium iodide, copper, iron, et cetera. Most reddish sweats, such as those seen in the axillary region, are due to the action of chromatogenic bacteria and are known as pseudochromidrosis. Murray[2] reported golden yellow perspiration and even yellow tears in a patient due to the absorption of a dye from face powder. The condition cleared up promptly two days after the use of the face powder was discontinued. Chromidrosis tends to appear in neurotic women, and frequently there is a history of a pelvic disorder. As a rule, hyperidrosis is not present.

The following case report is of interest:

Miss F. L. E., fifty-eight years of age, who has suffered from grass and ragweed pollinosis for forty-six years, associated with asthma for ten years, reported May 14, 1940, for grass and ragweed hyposensitization. There was nothing of note revealed at the physical examination with the exception of a few sibilant râles in both lungs. There was 4 per cent eosinophilia. There were large positive scratch reactions to giant and short ragweed, and burweed marsh elder; and positive intradermal reactions to grass pollen extract and house dust. Intradermal food tests were discontinued because of the excessive number of positive reactions but, by diet trial, the patient was found clinically sensitive to milk, rye and egg. Preseasonal ragweed hyposensitization was started, and later coseasonal grass hyposensitization was given with good results during the grass season and fair results during the ragweed season of 1940.

For the past eight to nine years this patient has noticed that about August 15 each year a "smudgy" bluish discoloration has appeared on her wash cloth. It begins gradually at the onset of the ragweed season and becomes more intense toward the peak of the season and gradually disappears by frost. Since 1941, dust hyposensitization has been given perennially, and preseasonal grass and ragweed hyposensitization has been repeated each year. A maximum dose of 5,000 units of grass has afforded excellent protection, while a maximum dose of 100 units of ragweed extract is all that tolerance permits. General reactions in the form of asthma occurred when this dose was exceeded; nevertheless, it has afforded fair

protection. Every year until this year, however, the discoloration of the wash cloth would begin with the advent of the ragweed season and continue until frost. It is not known whether this condition would occur in the absence of treatment, as injections of ragweed pollen extract have been repeated each year since 1935 because of the definite benefit afforded.

In 1945, without any alteration in the treatment schedule, the discoloration began about June 10, six weeks after ragweed hyposensitization had been started, when injections were given biweekly and a dosage of only 5 units had been reached. Following this, during an interval of two weeks, when no injections were given, the discoloration almost disappeared but reappeared in less intense form when injections were resumed at weekly intervals. For the past two years it has been impossible to exceed a dosage of 12 units of ragweed extract without inducing asthma, and yet the clinical results have been better than in previous years on a higher dosage. The bluish tinting continued all during the summer of 1945 in mild form but became markedly accentuated late in August and during the first two weeks in September and as usual disappeared by frost. Injections of ragweed extract were discontinued for the year on August 23, 1945.

COMMENT

During the time when the wash cloths are stained there is no discoloration seen on the skin or clothing or handkerchiefs, and there is no abnormal amount of perspiration. The wash cloths turn a deep inky blue when wet and impart to the water a slightly bluish tint. Later, the color turns blackish and remains so unless the cloths are boiled and bleached. Most of the color seems to come from the face, especially about the eyes, with lesser amounts from the axillary regions and groins. The amount of perspiration is a factor inasmuch as the discoloration is more marked in very hot and humid weather. It is difficult to understand why the discoloration began in June, 1945. It was unusually cool and rainy during this time, there was no excessive perspiration, and the dosage of ragweed extract was comparable to that given the year before. This patient is nervous, conscientious, and rather discontented. She had a myomectomy many years ago, but no menstrual difficulties followed and later there were no untoward menopausal symptoms.

No studies were made of the urine, but Dr. Smith Freeman of Northwestern University School of Medicine extracted from one of the wash cloths a blue substance that behaves chemically like indigo. Indican, which is a precursor of indigo, is a normal constituent of the urine. Indigo may exist in a blue or oxide form, or in a colorless or reduced form. It is possible that in this patient indigo was excreted in the colorless form and that the oxygen of the air or the chlorine contained in water may have initiated its conversion into the oxidized or colored form. Indole and skatole are formed normally in the large intestine and are due to the deaminization and decarboxylation of tryptophane by bacterial action.[1] Most of the indole is eliminated in the feces but small quantities are absorbed into the blood stream and are detoxified in the liver by conjugation with sulfuric acid and potassium or with glycuronic acid to form

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ALLERGIC CAUSES OF PRURITUS ANI

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THE following is a presentation of fourteen cases of pruritus ani seen by our allergy department. Most of these cases had been previously treated unsuccssfully by many methods, and show clearly that allergy is an important, neglected primary cause of pruritus ani.

The role of allergy in the production of pruritus ani has been described in a meager fashion for many years. It is not the intent of this paper to deprive the proctologists of their field of work. However, it is the intent of this paper to enjoin their co-operation in securing relief of a condition which is embarrassing, uncomfortable, and at times disabling. There has been very little literature associating pruritus ani with allergy. There has been only slight acknowledgment of the etiological relationship of allergy and pruritus ani in many commonly used textbooks on this subject to date. By definition, pruritus ani is an entity which subjectively consists of chronic or recurrent itching in the perianal region. The objective findings are usually excoriation, edema, thickening of the skin, and exudation in most cases. All of these, however, vary in degree and intensity.

Patients who have consulted us for relief of this symptom complex complain worse at night and have cycles of improvement and exacerbation. They have usually tried medications both locally and orally, some of these prescribed by the physicians and others by their neighbors. Many have tried x-ray, rectal dilatations, local injections, tattooing of the anal skin with anesthetics of protracted action, and many other surgical and semi-surgical procedures.

It is desirable to emphasize to you that this presentation is intended not only to place a large number of these conditions in their proper places from an etiological standpoint, but to simplify their therapy after having once determined their etiology. Much has been written regarding the presence of pH alterations (Slocumb[5]), (Davis[4]); mechanical factors (Buie[1,2]); chemical disturbances (Tucker[6]). We maintain that we have frequently observed changes which we originally felt were primary to be secondary to allergy.

The best classification from the standpoint of etiology is taken from Cantor's[3] paper. It is introduced to give you the present scope of the extensiveness of causes.

As we review the classification dealing with cryptogenic pruritus ani, local, psychogenic, traumatic, thermal, chemical and other types of rectal diseases, it is certainly difficult at times to place them as a primary cause. Even the presence of local growths of yeast, fungus, and Trichomonas can be predisposed to by the presence of weeping, allergic eczemas of the anus.

SPECIFIC ETIOLOGICAL CLASSIFICATIONS

A. Cryptogenic pruritus ani—usually associated in vicious cycle with relief trauma (i.e. scratching)

B. Local Rectal
1. Rectal constipation
2. Fissure
3. Fistula
4. Cryptitis and papillitis
5. Proctitis

Factors
Mechanical (Traumatic)
Chemical
Bacterial, *with later possibility* of allergic and psychogenic complicating factors

C. Psychogenic
1. Hysteria
2. Anal masturbation
3. Other psychoses

D. Traumatic

1. Scratching	Mechanical
2. Rubbing of clothing	Mechanical

E. Allergic
1. Sensitization to bacterial toxins, fungi, or focal infections
2. Foods
3. Drugs, et cetera
4. Eczemas

F. Parasitic
1. Pinworms
2. Trichomonas
3. Monilia
4. Fungi
5. Itch mites

G. Thermal—warmth and associated perspiration (moisture)

H. Chemical
1. Chemical in diapers (washing): Infant pruritus
2. Alkaline or acid urine
3. Self or prescribed medications
4. Sweat
5. Urine containing calcium or oxalate crystals
6. Urine of senile dribbling

I. General Metabolic
1. Thyroid dysfunction
2. Diabetes
3. Kidney disease
4. Liver disease
5. Anemia
6. Vitamin deficiencies

J. Reflex (?)

TABLE I

	DURATION AND PREVIOUS TREATMENT	SOURCE OF ALLERGEN SUGGESTED BY	STUDIES	CONFIRMATION AND TREATMENT
Case 1. W.W. Male 30 yrs. 2-3-39	4 yrs. intermittent Medicine & x-ray Dilatation Alcohol injection Hemorrhoidectomy	History	Not done	Elimination diet Proved fish
Case 2. R.A.M. Male 32 yrs. 2-3-39	2 mos. intermittent Medicine X-ray	History	36 food tests all less than 2+ Blood eosinophilia Avocado patch test pos. at 4th day. Neg. 48 h.	Proved by elimination and inclusion. Patch test remained positive for several weeks.
Case 3. W.L. Male 29 yrs. 4-21-43	9 yrs. intermittent Medicine, x-ray Rectal dilatation	Routine studies	30 foods and 6 misc. Pork 3+, beef 3+ 4 other 2+ Eosino. 3+ pH 7.8	Elimination diet proved beef Patch test pos. after 5 days. Symptom free 2½ years
Case 4. G.C.S. Female 35 yrs. 5-25-43	20 yrs. constant Injection of hem. Fistula operation Medicine & diet Colonic irrigation	Routine studies	32 foods Wheat 2+, prunes 2+ Apples 2+, green peas 2+	Elimination diet. Symptoms cleared after 1 wk. Returned 7 to 10 days after beginning wheat. Patch pos. after 4 days.
Case 5. E.A.F. Female 44 yrs. 5-30-43	2 to 3 mos. Medicine locally	Routine studies History	34 foods—dewberries 4+ Beef 3+, w. potatoes, beets, yeast 2+ Eosino. +, pH 8	Elimination diet No recurrences Yeast in smears cleared up without local treatment
Case 6. F.R. Age 35 yrs. 7-4-43	2 yrs. seasonal Medicine	History Migraine for 1 yr.	20 foods—figs, wheat 3+. Others O	Diet proved figs. Migraine due to chocolate, fish and onions. Patch: acetone neg. Water pos. 3 days.
Case 7. G.S.R. Female 43 yrs. 4-14-44	10 yrs. constant (Pt. ashamed to tell doctor.) Medicine	History Eczema on hands	40 tests. Six 3 & 4+ reactors. Mold, H.D., staph. & pyreth. 3 & 4+ pH 7.6, eosino. pos.	Diet proved chicken 2+, string beans and rice 3+, Eczema and pruritus ani healed simultaneously.
Case 8. J.F.Mc. Male 74 yrs. 5-18-44	Constant 1 mo. None	History of Rx. Dysuria (associated)	10 foods 9 were 4+ 1 was 3+ Apexol—4+ patch test after 4 days	Elimination diet—no relief Sensitive to all C.L.O. Patch test pos. 3 weeks

TABLE I. (continued)

	DURATION AND PREVIOUS TREATMENT	SOURCE OF ALLERGEN SUGGESTED BY	STUDIES	CONFIRMATION AND TREATMENT
Case 9. L.L.H. Male 27 yrs. 10-14-44	3 years constant Medicine	Routine studies	24 skin tests Spinach 3+ 6 others 2+ Potatoes 2+ Eosinophiles pos. pH 8	Elimination diet proved potatoes Patch test pos. after 48 h. Present for 3 more days
Case 10. R.J. Male 37 yrs. 1-10-45	3 or 4 years Occasionally Medicine	History	20 foods all 1+ or neg. Patch test for peanut oil pos. 48 h.	Elimination and inclusion
Case 11. W.E.T. Female 38 yrs. 1-25-45	Many years Constantly Medicine	History and relief after colostomy Later eczema on abd. Patient blamed milk	Skin tests not done	Elimination and inclusion proved cause to be milk
Case 12. G.H. Male 43 yrs. 2-5-45	In summer for 2 or 3 years Medicine	Worse when feet had "athlete's foot"	20 foods negative Contactants negative Trichophyton 3+ Eosinophiles positive Fungus neg. locally	Feet treated Trichophyton desensitization Patient relieved
Case 13. G.P. Male 44 yrs. 9-3-45	5 mos. constant Medicine Injection hem. Hemorrhoidectomy X-ray therapy	Routine studies	14 foods Beef 3+ Egg 3+ Others 1 or 2+ Eosinophiles pos. pH 7	Elimination diet confirmed eggs
Case 14. V.B.H. Male 44 yrs. 10-7-45	Duration 6 years const. Medicine Hemorrhoidectomy Fistula operation X-ray therapy	Routine studies	30 foods tested Most of them 2,3,4+ B. Coli 4+ Eosinophiles pos. pH 7.2	Elimination diet gave no relief Sulfaguanidine—improved Desensitization gave most relief

The anal skin is most often moist, excoriated and incompletely cleansed, and this makes it ideal for entrance of antigen into the skin.

In our more recent cases, we have made the following routine studies:

1. Careful history of the condition with reference to duration of symptoms, the type of diet, medicines, infections and other allergic exposures.
2. Proctoscopic and prostatic examination, including study of prostatic exudates.
3. Rectal smears for eosinophiles, determination of relative pH by the use of litmus paper, scrapings for worms and miscroscopic examination for the presence of yeast, molds and trichomonads.
4. Complete blood count, blood Wassermann, urine and stool.
5. Allergic survey, being careful to rule out all contactants in addition to ingested allergens.
6. The careful use of food diary and diets to eliminate or incriminate the suspected food.

The presentation of cases in Table I represents only a small series and is not presented for statistical value. At the same time, without exception, these cases have represented the ultimate success in management of fourteen cases after all other measures have failed. In investigating some of of the earlier cases, it will be noted that some of the procedures which are routinely carried out at this time were omitted. That was due in part to our lack of understanding of the causes as we now see them. Please note that in a large number of cases the patient has suggested the offending allergen.

To summarize the conclusions which may be drawn from the above cases:

1. Careful attention to history is an important diagnostic help.
2. Elimination diet, food diary and trial and error investigation must be resorted to in every case.
3. The skin tests appear helpful in some cases, and latent reactions are more significant than early reactions.
4. Pruritus ani may be a contact condition, as suggested by patch tests and the colostomy patient.
5. Exudates from anal margins contain many eosinophils when allergic causes are present.
6. Allergic causes of pruritus ani should be investigated before radical procedures are suggested, such as surgery, x-ray, injections, division of nerves or tattooing of the anal margins with anesthetics.
7. Diagnoses of psychogenic and neurotic etiology are often erroneous.
8. Cryptitis, papillitis, pH changes, fissures are often secondary instead of primary changes.

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THE QUANTITATIVE LEPROMIN TEST IN LEPROSY

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THE lepromin test was described by Mitsuda in 1923. Since then numerous works have been published dealing with its value in the diagnosis and prognosis of leprosy. With regard to the first point, there have been many discussions concerning the immunological character of the response and its specific or non-specific basis, the relative value of early readings (twenty-four to forty-eight hours) or late ones (seven, fourteen and twenty-one days) and finally the relative importance of the morphological characteristics of the cutaneous response itself (erythema, nodule, necrosis).

The aim of the present work is to analyze the reactions observed in normal non-lepers, as well as in lepers of the different forms, following the intradermal injections of lepromin in different dilutions (quantitative reaction), care being taken to record the reaction during the first twenty-four to forty-eight hours and at seven, fourteen and twenty-one day intervals recording all skin changes—observed (qualitative reaction).

MATERIAL AND METHODS

1. In preparing Mitsuda's antigen, Muir's modification was followed, nodules were obtained preferably from the ear lobe of leprous patients of the lepromatous form. The nodules were boiled in water for twenty minutes, cut into small fragments and the epithelium removed.

The material was dried in the air current of an electric fan for several hours and then placed in a dessicator and dried over concentrated sulphuric acid. When completely dry, the material was powdered in a mortar and kept dry, sufficient material having been prepared to insure uniformity in the results throughout the experiment.

2. Suspension of the antigen was made as follows: 400 mgms. of the dry powder were triturated with 10 c.c. of saline solution, the suspension drawn off, and the residue was again triturated with the same amount of saline and the resulting suspension again drawn off. This process was repeated three or four times. The pooled suspension was shaken in a flask and allowed to settle for ten minutes, the liquid decanted and the sediment set aside. The volume was made up to 100 c.c. with saline and phenol 0.5 per cent. The antigen thus obtained was bottled and sterilized by autoclaving at 120 C. for thirty minutes. Using sterile technique, dilutions of the original antigen in saline were made to obtain suspensions at 50 per cent, 20 per cent, 10 per cent and 1 per cent. Part of the undiluted antigen was set aside to be used as a 100 per cent suspension.

3. Intradermal tests were made by injecting 0.1 c.c. of the above dilutions in the outer aspect of the arm, separate syringes being used

for the different concentrations. The concentrated (100 per cent) antigen was always injected into the upper part of the arm, and the dilutions in decreasing strength in corresponding lower positions.

4. Recording of skin responses:

Individuals were observed twenty-four and forty-eight hours following injection and at intervals of seven days over a period of three weeks. Infiltration was measured with a millimeter scale and the morphological alterations such as pustules or necrosis were recorded. Hayashi was the first to try to standardize and correlate the degree of reactivity from slight to strong reactions, with nodules from 2 mm. to more than 10 mm. and formation of pustules. Rothberg studied some 1,000 lepers and stated that positives (meaning immunological defense) should be accepted only if nodules of more than 5 mm. were formed at the end of the third week. In our work, any significant change in the skin response was recorded and a positive reading was taken to be any infiltration greater than 1 mm. in diameter.

Studies were made along the above lines in forty-six "healthy" non-leprous adults of both sexes taken from the wards of the General Hospital, and sixty lepers, thirty-nine of which were of the lepromatous and twenty-one of the tuberculoid form. The clinical study of the patients was kindly made by the medical staff of the Dr. Pedro Lopez Dispensary for Lepers of Mexico City.

RESULTS

The result obtained in the "healthy" group, are clearly demonstrated in Figure 1.

Readings made in forty-eight hours revealed 97.8 per cent positives with the concentrated antigen. The mean was 6.8 mm., necrosis was noted in 4.4 per cent. Positivity decreased to 32.6 per cent with the 1 per cent antigen (mean 3 mm.). No necrosis was observed from the dilutions. Late readings (seven, fourteen and twenty-one days) were somewhat less positive but necrosis was higher reaching: 7.7 per cent (seventh day), 18.9 per cent (two weeks) and 20 per cent (three weeks) with the full strength antigen.

The lepromatous lepers (thirty-four cases), behaved quite differently. The concentrated antigen gave 79.5 per cent positives in forty-eight hours. The mean was 7.2 mm., necrosis was noted in 33.3 per cent, but quantitatively a response was observed with difficulty in using the 10 per cent antigen. No reactions were observed after injecting the 1 per cent antigen (Fig. 1). On the seventh day, more striking results were observed. There was a decrease in the size of the previous papules, and there was no local reaction to the 20 per cent antigen.

Readings taken on the fourteenth day gave only one positive to the 100 per cent antigen consisting in a five mm. nodule with necrosis. This

same case was the only positive on the twenty-first day, the nodule having acquired a size of 6 mm. No responses were elicited from the antigen dilutions during these two periods of observation.

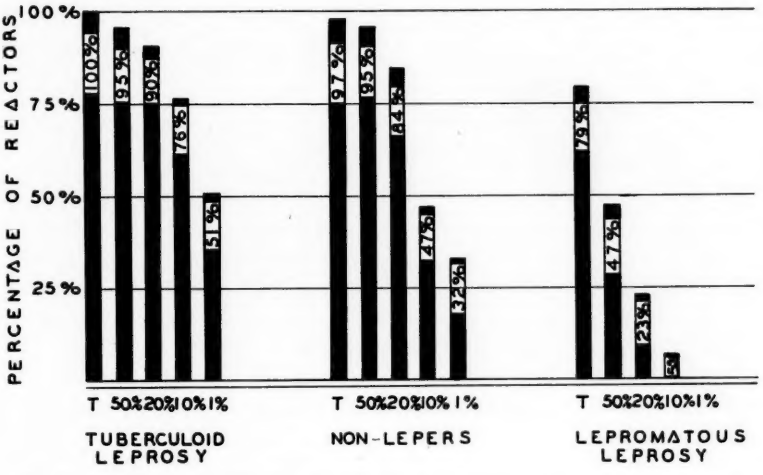

Fig. 1. Mitsuda reaction—readings at forty-eight hours. Quantitative responses in the different groups of leprosy and in non-lepers.

The most interesting results were obtained in the tuberculoid form of leprosy as shown in the Figure 1. There were 100 per cent positives to the concentrated antigen in the forty-eight-hour interval with a mean of 9.2 mm. Necrosis was observed in 14.2 per cent and 10 per cent with the 100 per cent and 50 per cent dilutions respectively. There were 57 per cent positives obtained using the 1 per cent antigen dilution with a mean of 5.2 mm. The erythema observed in the forty-eight-hour reading groups was marked and pustules were frequent. On later readings, infiltration was attenuated but the incidence of necrosis increased to 70 per cent witth the concentrated antigen in the three-week period. Necrosis was evident in 20 per cent of the individuals after reaction to the 1 per cent antigen at the same time interval.

DISCUSSION

From the data presented it is readily observed that the Mitsuda test behaved in an entirely different manner in tuberculous and lepromatous individuals regardless of the time when readings were taken. Authorities agree on this point, but many physicians hesitate to concede any value to the twenty-four to forty-eight hour responses stressing the morphological (qualitative) changes observed typically in later observations (nodules, pustules, and necrosis). In our cases, however, a clearcut difference was

observed between the tuberculoid and lepromatous patients when readings were taken at forty-eight hours. Figure 1 shows that with the quantitative test, lepromatous patients failed to react to the 1 per cent dilution, while in the tuberculoid individuals, 50 per cent positives were obtained with

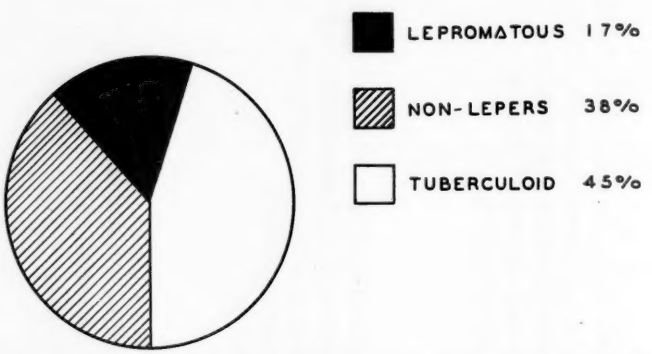

Fig. 2. Mitsuda reaction—readings at forty-eight hours. Qualitative measure (area of positive skin response) or reactions at forty-eight hours in the different groups of leprosy and in non-lepers.

the same antigen dilution. It may also be seen that the percentage of positives ranged from 100 per cent (tuberculoid) to 79.5 per cent (lepromatous), using the concentrated antigen. The 10 per cent antigen resulted in 76 per cent and 5.8 per cent positives in the tuberculoid and lepromatous cases respectively.

If one considers the size of the responses as observed in the 48 hours reading and expresses the sum of the average mean in each group of individuals taken in percentages, the result as seen in Figure 2 leaves little doubt as to the larger skin area response of the tuberculoid group.

The response in normals, considered positive in many cases by most authorities is quantitatively and qualitatively more intense than in lepromatous cases. Thus it may be assumed that the early, twenty-four to forty-eight hours, responses, drawing an immunological parallel with the tuberculin test, could be interpreted as strictly specific to reveal primary sensitization. Then non-lepers would give the normergic positive response while tuberculoid patients would represent the hyperergic individuals, lepromatous then being the hypoergic or anergic group, low response and tendency to necrosis (33 per cent) being comparable to that seen in cases of some skin negative tuberculoids with anergy (negative tuberculin papulo necrotic tuberculids).

CONCLUSIONS

1. A study was made of the Mitsuda reaction principally in its early forty-eight-hour manifestation. The clinical material consisted of forty-

six non-lepers, and sixty lepers, thirty-nine of which were of the lepromatous and twenty-one of the tuberculoid form.

2. Quantitative tests were conducted using the antigen in dilutions ranging from 100 per cent to 1 per cent. The morphology of the reaction was considered as a qualitative response.

3. The tuberculoid patients responded in over 50 per cent of the cases to the 1 per cent antigen, the weakest employed. Non-lepers reacted in one-third of the cases, while lepromatous patients failed to react to the same dilution.

4. There is a strict correlation between the intensity of the early, forty-eight-hour response and the late (two or three weeks) development of the necrotic reaction.

5. The average mean diameters of responses seen at forty-eight hours with the 20 per cent antigen dilution were as follows: 3.7 mm. for non-lepers, 2.8 mm. in lepromatous patients, and 10.2 mm. in the tuberculoid forms.

6. It is proposed that if the response obtained in forty-eight hours in non-lepers is taken as normergic, tuberculoids should be considered as hyperergic and lepromatous individuals as hypoergic reactors.

7. Adopting the above criteria for the Mitsuda reaction, there should be no difficulty in considering the same as within the group of the tuberculin (infectious) type of allergy.

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COLLEGE REGIONAL SPRING CLINICAL COURSE IN ALLERGY

The Mississippi Valley Sectional Instructional Course in Allergy for physicians wishing to refresh their knowledge of the subject and those training for specialization in Allergy will be held under the auspices of the University of Kansas School of Medicine, Kansas City, Kansas, May 5-7. The hours will be from 9 to 12:15 and from 2 to 5:15. This course is for the purpose of acquainting physicians with the fundamentals of diagnosis and treatment of allergic diseases. There will be a round table discussion and every phase of allergy will be presented. The schedule, faculty and detailed information will appear in the November-December ANNALS. The fee is $35.00.

For details write to Dr. Orval R. Withers, Suite 1418 Bryant Building, Kansas City 6, Missouri.

CONTACT DERMATITIS FROM JAPANESE RIFLES

LT. FRANK HINMAN, JR., MC, USNR

A Japanese rifle was secured for each of ship's company during the stay of this aircraft carrier in Tokyo Bay. These were distributed during a three-week period. An estimated 150 recipients refinished the stocks of their guns, using scrapers and sandpaper. Gloves were not worn and hands were merely washed with soap and water. Seven officers and men subsequently suffered skin lesions severe enough to consult the medical department; of these, two required hospitalization in sickbay. The incidence of dermatitis among those exposed was slightly over 4.5 per cent.

CASE REPORTS

Case 1.—A twenty-two year old pilot had a history of marked sensitivity to poison ivy allergens with a decrease after desensitizing injections, of a recent severe episode of poison oak dermatitis, and of hives on eating shellfish. He sanded his rifle while dressed in shoes, shorts, and skivvie shirt. Two days later he noted a vesicular eruption on the palms of his hands and between the fingers, followed by a similar eruption over the elbows, in the antecubital fossae, on the thighs, and over the ankles. The lesions closely resembled poison oak dermatitis in their grouped vesicles and severe itching. The patient was treated with warm magnesium sulfate soaks and was discharged in five days fit for duty.

Case 2—A thirty-eight year old gunnery lieutenant commander stated that he was very susceptible to poison ivy dermatitis, as were his parents and brothers. Two days after sanding his rifle, he noted persistent itching, then the formation of vesicles on the palms and between the fingers of both hands. These lesions subsequently oozed, then became crusted and edematous. He was treated with plain calamine lotion and was well after six days.

Case 3.—A twenty-two year old lieutenant had a history of hay fever every summer from common pollens, and had had occasional eruptions from contact with poison oak leaves. His sister had bronchial asthma. A little more than two days after he sanded his rifle, he noted the typical itching vesicular lesion on the palm, dorsum, and between the fingers of each hand, similar to that he had seen develop on the hands of his shipmate, Case 2. The lesion was treated with calamine lotion without phenol, and although the swelling was marked, it cleared in eight days.

Case 4.—This twenty-five year old Chief Machinist's Mate had always been very susceptible to poison oak allergens.He stated that just walking near the plant was sufficient to cause dermatitis. Two days before being seen, he was sanding rifles. The following day he noted a vesicular eruption between the fingers of both hands and on the flexor surface of the left forearm, accompanied by severe itching. The lesions were treated with calamine lotion and cleared after five days.

Case 5.—A twenty-four year old lieutenant had had occasional attacks of moderately severe dermatitis from contact with the poison ivy plant, but there was no other history of allergy in himself or his family. Two days before the onset of the lesion, his roommate sanded his gun and distributed varnish about the room.

The patient believes that he inadvertently rubbed some of it onto his face. The lesion appeared on the cheeks beneath the eyes, was slightly vesicular, and was accompanied by itching and marked edema. Without approval of a medical officer, he was treated for one day with ammoniated mercury ointment, which caused the

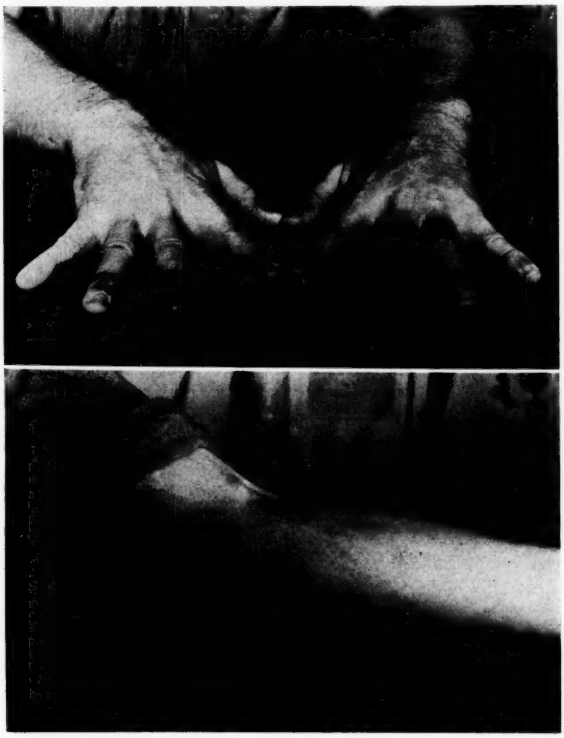

Fig. 1. Case 4: The distribution of the characteristic vesicular lesions is readily seen on the far right.

Fig. 2. Case 4: Grouped vesicles on the flexor surface of the left forearm.

lesion to spread. Warm magnesium sulfate soaks were begun, with application of calamine lotion in the intervals, and the lesions subsided in 10 days.

Case 6.—A twenty-two year old second-class aviation ordnanceman stated that he had hay fever every summer and was very susceptible to poison ivy allergens. For three days he took apart and reassembled his rifle, without sanding. The day after completing this, he noted a vesicular rash principally between the first and second digits of his left hand, in the web space. Similar smaller lesions appeared in the web spaces between the second and third, and the third and fourth digits of the left hand. His right hand remained normal. The eruption was treated with calamine lotion and cleared after six days.

Case 7.—This twenty-four year old pilot had severe ivy poisoning as a child, but stated that he had not been exposed since. Every fall he had had allergic rhinitis. His only sister is sensitive to poison ivy allergens and experiences "rose fever." He sanded his rifle while fully dressed and two days later he noted a

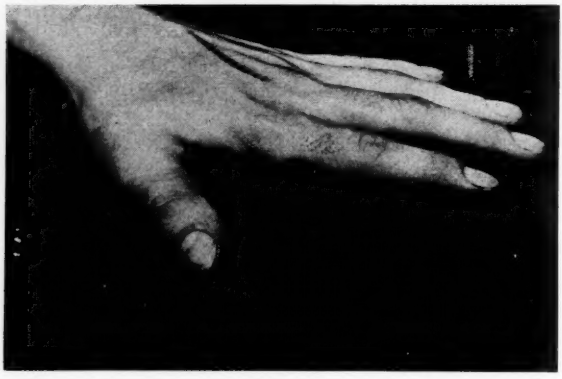

Fig. 3. Case 6: Typical vesicles in the web spaces.

vesicular lesion on the flexor surfaces of his wrists, and later developed similar lesions about the axillae, ankles, genitalia, and knees. He had changed his clothes several times in the stateroom in which sandpaper dust had settled. The eruption, so severe that hospitalization was necessary in sickbay, was treated with continuous warm wet packs and cleared in six days.

REPORT OF CONTROLS

Seven men who worked in the ship's armory and therefore had been cleaning and handling these rifles during the period under study, were interviewed. None of these men had noted itching or eruption. They had had no previous attacks of poison oak dermatitis (except two who had it only as small children) and no history of allergic disease in themselves or their families. Hospital corpsmen, selected for negative allergic histories, were observed refinishing rifles without incidence of dermatitis.

DISCUSSION

This outbreak apparently represented the result of intimate contact with a special varnish in individuals with known sensitivity to certain allergens. In Japan, the common natural varnish is obtained from the sap of *Rhus vernicifera,* a species of sumac. The varnish implicated in the present episode has not been positively identified as sumac varnish, although the high incidence of history of sensitivity to the related *Rhus toxicodendron* is suggestive. Before the war, medical officers of ships stationed in China observed that contact with new lacquerware by seamen on liberty caused a similar vesicular dermatitis, known locally as "Ningpo Poisoning." The

itching, vesicular nature of the lesion, its characteristic distribution on the hands and other sites of contact, its onset two days after a definite and usually single exposure, and its response to removal of the exciting agent and to mild treatment indicates that the Japanese varnish on the rifles caused a contact dermatitis.

Patch tests were not performed because of the evidence that the varnish was the etiological agent and because the approach of the ship to the continental United States made the possibility of exacerbation of the disease inadvisable.

SUMMARY

Seven cases of itching vesicular dermatitis, usually on the hands and forearms, occurring two days after intense exposure by sensitive individuals to the sanded varnish of captured Japanese rifles, have been observed during a two-week period. The lesions responded readily to removal of the allergen and local treatment. Since many of these rifles are in the hands of men returned from overseas, scattered cases will probably be seen throughout the country. Care should be used by individuals with known sensitivity to plant and other allergens, and that of poison oak or ivy in particular, when handling articles coated with Japanese lacquer or varnish.

Chromidrosis Associated with Ragweed Hyposensitization

(Continued from Page 373)

potassium indoxyl sulfate or indican which is excreted in the urine. There is no reliable evidence that indican, even in relatively large amounts, produces any signs of toxicity. Amounts given by mouth greatly exceeding those present normally in the bowel produce no symptoms.

The discoloration of the perspiration in this patient is probably due to indigo. The question arises as to whether this reaction is peculiar to this patient or whether it may be present in other patients to a minor degree.

SUMMARY

A case of chromidrosis is reported occurring in a patient with ragweed pollinosis during the course of ragweed hyposensitization.

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ALLERGIE

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IN recent years a series of facts has been collected which belongs to the realm of immunology but which, however, does not fit well into this category; these are the discoveries of hypersensitivity in the immunized organism.[1]

These two terms are blatantly contradictory. When we speak of immunity we think of an organism protected against a disease. How is it that he simultaneously should be hypersensitive to the same disease?

This contradiction was already felt by von Behring when he designated as a "paradoxical reaction" the death of animals, previously highly immunized against tetanus, from small doses of the same toxin.

A "paradox" of course, could only be accepted as an exceptional occurrence; the more, however, one investigates the subject the more he realizes the regularity of this phenomenon. By this time we know already a great number of pathological conditions where symptoms of hypersensitivity are encountered. To this group belong: Tetanus (von Behring, Kretz). Tuberculosis (Courmont, Strauss and Gamaleia, Babes and Proca, Detre-Deutsch, B. Schick, Lowenstein and Rappaport, Moller, Lowenstein and Ostrowsky). Syphilis (Finger and Landsteiner). Diphtheria (Rigt). Serum (Arthus, von Pirquet and Schick, Lehndorff, B. Otto, Rosenau and Anderson). Bacteria in general, organ extracts, various proteins, hay fever (A. Wolff-Eisner).

Is it true that immunity and hypersensitivity are actually combined with one another or are the processes in which previous treatment causes immunity to be separated from those in which it leads to hypersensitivity?

A. Wolff-Eisner[2] intends to carry through the distinction as follows: processes in which toxins are involved lead to the production of antitoxins and immunity; processes in which endotoxins represent the effective agent lead to hypersensitivity.

We see, however, from the experiences with tetanus that hypersensitivity may occur even in exclusively antitoxic processes. The objection of Wolff-Eisner that this is only an exceptional occurrence does not appear to me to touch the essential problem.

Richet[3] who was the first to ascribe an important significance to hypersensitivity which he called anaphylaxis found that injection of an actinium poison produced simultaneously immunity and anaphylaxis: If the injection of the poison was repeated after a certain time interval, the animals usually met with a sudden death. However, if they lived through the

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Read by Dr. French Hansel at the annual meeting of the American College of Allergists, June 1946, marking the fortieth anniversary of the appearance of the original article.

first shock then they overcame the disease more rapidly than control animals injected but once.

Similar ideas were developed by von Pirquet and Schick[4] concerning serum sickness. The phenomena following reinjection show a more violent and more rapid course.

Recently Rosenau and Anderson[5] have shown that in spite of the enormous hypersensitivity acquired by guinea pigs following injection of minimal amounts of horse serum, immunizing processes were found to be simultaneously associated therewith; if the injection, instead of being done but once, is repeated for ten days, the ten times injected animal does not succumb to the reinjections of horse serum in contrast to the singly injected animal.

The combination of immunity and hypersensitivity appears most evident from the experience with vaccination.[6] The individual previously vaccinated compared to one vaccinated for the first time appears hypersensitive, because he reacts more quickly to the infection and at the same time he is protected. The vaccination causes in him only a small local reaction. He is spared all general symptoms.

Similar conditions in syphilis have been revealed recently by Finger and Landsteiner.[7] The reinoculation with syphilis has a distinct effect in all stages. This effect presents itself faster than in the case of a first infection; in other words, the incubation period is shorter. In tertiary syphilis reinoculation may be followed immediately by a local erythema, a process which may be regarded as identical with the "immediate reaction" following repeated serum injections.

Immunity and hypersensitivity, therefore, can be connected most intimately with one another.

These terms are, however, contradictory. Their union is a forced one. The concept of immunity, of course, goes back to the time when hypersensitivity was yet unknown.

However, as F. Hamburger[8] says, the specific alteration which an animal suffers after an experimental disease almost as frequently consists of an increased sensitivity as it consists of an increased resistance.

We require a new general term which prejudices nothing, a term to designate the alteration which occurs in the organism when it comes in contact with any organic living or lifeless poison.

The vaccinated individual reacts to the vaccine, the luetic to the virus of syphilis, the tuberculous to the tuberculin, the individual injected with serum reacts to the serum differently than an individual who has not yet been in contact with the respective agent; yet he is far from being not sensitive. All we can say about him is that his capacity to react has changed.

For this general concept of the *changed capacity to react* I suggest the term *Allergy*. Allos designates the deviation from the original condition, from normal behavior, as in the words allorythmia and allotropy. The

vaccinated, the tuberculous, the individual injected with serum become *allergic* with regard to the respective foreign bodies. A foreign body, in turn, which conditions the organism to a change of reactivity as a result of one or more incorporations is to be called an *allergen*. The term is formed as an analogy (in an, of course, not philological manner) to the term antigen (Detre-Deutsch). This latter term designates a substance which is capable to produce antibodies. The concept of allergen is more far reaching. It includes in addition to the antigens numerous protein bodies which do not produce antibodies but cause hypersensitivity. Everything which causes diseases followed by immunity is to be regarded as an allergen. There are also to be included in this category the poisons of mosquitoes and bees insofar as they are followed by signs of hypo- or hyper-sensitivity. For this reason we have to include in this category the pollens of the hay fever (Wolff-Eisner), the urticaria producing substances of the strawberries and crabs and probably also a series of organic substances which lead to idiosyncrasy.

The term immunity should be restricted to those processes in which the incorporation of the foreign substance does not produce any clinical reaction, where, therefore, complete insensitivity is present. It makes no difference whether this be caused by alexins (natural immunity), by antitoxins (active and passive immunity against diphtheria or tetanus), or by a sort of adaptation to the poison (Wassermann and Citron).

The new terms do not interfere with the present nomenclature. The sharply defined concepts of antitoxin, cytolysin, hemolysin, precipitin, agglutinin, coagulin are not disturbed thereby. Hypersensitivity is a new field of research in which only during the last few years the formation of the concepts occurred by a painful adaptation to the old terms.

In order to bring clarity into the development of these concepts, I suggest these new designations. I hope that by this simplification of the external forms I shall facilitate the study of these interesting phenomena for new students in this field.

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BRONCHIAL ASTHMA IN THE YOUNG MALE ADULT

A Study of Fifty Patients Returned from the Tropics for Bronchial Asthma, as Compared to Fifty Asthmatics Stationed in the United States

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THE purpose of this study is to discover what differences in findings, if any, exist in a group of patients returned from tropical areas for asthma as compared to an equal number of perennial asthmatics who never left the borders of the United States.

These patients were admitted to the allergy ward of Wakeman General Hospital, Camp Atterbury, Indiana from August, 1944 to November, 1945. The group consisted entirely of enlisted men, with ages ranging between eighteen and thirty-nine.

That asthma has been a common cause of tropical medical casualties has been noted by many medical officers. Winkenwerder[18] reported that asthma represented 1.2 per cent of total admissions at a general hospital in the Southwest Pacific area. One typical evacuation order from that region returned twenty-four asthma patients to the United States out of a total of two hundred and twenty-nine medical casualties of all kinds.

The fifty patients in this study were all returned from the Southwest Pacific. They were evacuated either by ship or plane from New Guinea, Fiji, New Caledonia, New Hebrides, Hawaiian Islands, Solomon Islands and Northern Australia. Their tour of tropical duty ranged from three days to eighteen months, with an average for the group of about six months.

Army service in the home group varied from one week to five years, with a group average of about eighteen months.

INCIDENCE OF FIRST ASTHMA ATTACK

In the group returned from the tropics, twenty patients (40 per cent) had the first attack of asthma while in that area. In the U. S. group only seven (14 per cent) had their first attack of asthma after army induction. Almost three times as many soldiers in this series had their first attack of asthma in the tropics as compared with the incidence among those stationed in the United States. Leopold[7], reporting on a group of soldiers from all overseas theatres, states 31.5 per cent developed the initial attack of asthma overseas.

In the group of tropical asthmas now being considered, it was not uncommon to find a soldier who had had no asthma for ten to fifteen

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TABLE I. X-RAY OF CHEST: POSITIVE FINDINGS

Fifty U. S. Asthmas		Fifty Tropical Asthmas	
Case Number		Case Number	
9	Moderate exaggeration broncho-vascular markings throughout.	45	Exaggeration broncho-vascular and hilar markings bilaterally, one week later normal.
92	Productive changes both lower lobes, result of previous lipiodol.	80	Accentuation of lung markings suggestive of pulmonary irritation.
94	Increased broncho-vascular markings.	93	Slight exaggeration broncho-vascular markings.
107	Productive changes both lower lobes, results of previous lipiodol.	123	Marked accentuation broncho-vascular markings, two weeks later normal.
112	Increased broncho-vascular markings.	132	Partial obscuration left costophrenic sinus, one week later normal.
129	Exaggeration broncho-vascular markings with some linear fibrotic changes at right first intercostal space.	125	Broncho-vascular markings exaggerated. Small calcified primary tuberculous complex right upper lobe.
134	Exaggerated broncho-vascular markings.	178	Moderate increase in broncho-vascular markings.
144	Exaggerated broncho-vascular markings.	150	Moderate increase in broncho-vascular markings. Three weeks later normal.
3	Slight central thickening and accentuation root branches toward left lower lobe.		

years, then had had severe attacks within days or weeks after arriving in New Guinea, whereas in the United States group it was rare to find such cases.

BLOOD EOSINOPHILS

Three smears were taken on each patient at weekly intervals. In the home group the average of these three ranged from 1-12 per cent, with sixteen (32 per cent) having an average blood eosinophilia of 5 per cent or more. In the tropical group the average ranged from 0-15 per cent with 21 (42 per cent) having blood eosinophilia. All patients who had eosinophilia of 5 per cent or over received three stool examinations for ova and parasites. Both groups were entirely negative.

Tropical service *per se* did not seem to cause eosinophilia. A control group of fifty malaria and upper respiratory patients recently returned from the tropics had only two patients with an average eosinophil count over 5 per cent.

X-RAY OF CHEST

All patients received an admission x-ray of the chest interpreted by the chief of the x-ray service. If findings were positive re-rays were taken at weekly intervals.

The slightly greater degree of eosinophilia encountered in the tropical group suggested the possibility that more positive chest x-rays might be present in this group, in the light of reports[1,3,5] in the literature of tropical eosinophilia with positive chest x-ray findings. However, there

was no essential difference in the chest x-rays of these two groups (see Table I). Forty-two of the tropical group had normal plates, as did forty-one of the United States group. There was no relationship between the eosinophilia and the chest x-ray findings.

TABLE II. SKIN TESTS (INTRACUTANEOUS)

	Fifty Tropical Asthmas	Fifty U. S. Asthmas
Dust (1-1000)	6	9
Timothy	21	13
Alternarius	5	3
Feathers	3	12
Orris	6	5
Dog Dander	2	4
Ragweed	19	16
Horse Dander	2	8
Silk	4	5
Glue	1	5
Hormodendrum	2	2
Cat Dander	1	2
Tobacco	2	3
Horse Serum	7	4
Pyrethrum	4	3
Wool	0	0
Kapok	3	0
Egg white	3	7
Milk	10	11
Beef	8	11
Wheat	2	2
Chicken	3	8
Tomato	3	4

SKIN TESTS (INTRACUTANEOUS)

Lederle extracts in accepted dilutions were used in this series. Dust, tobacco and molds were obtained from Abbott Laboratories. A wheal of at least 0.5 to 1 cm. was necessary for a slight positive reaction, 1 to 2 cm. for a moderate reaction, 2 cm. for a marked reaction.

While the number of positive reactors in each of these groups is not large enough to draw positive conclusions, still the differences in some of the tests may be of enough significance to warrant further study (see Table II). For example, 42 per cent of tropical patients reacted to timothy, while only 26 per cent of the U. S. group did. Only 6 per cent of the tropical asthmas reacted to feathers, while 24 per cent of the U. S. group were positive. The latter group were in contact with feather pillows in the United States, whereas the overseas troops rarely enjoyed this luxury.

There were less positive reactions to the common foods in the tropical group, which may be explained by the fact that overseas troops usually subsist on canned, less allergenic foods.

It is common knowledge how rapidly everything becomes moldy in the tropics. This suggested the possibility that molds may be an important factor in the production of "tropical asthma." However, in this series the molds *Alternarius* and *Hormodendrum* produced disappointingly few positive reactions, though slightly higher in the tropical group. Perhaps the Southwest Pacific molds have an uninvestigated specificity.

DISCUSSION

Why does asthma occur so much more frequently in American soldiers in the Southwest Pacific than among those in the United States? Text books on tropical medicine contain little or no allergic studies of these islands. In a recent text[13] bronchial asthma or "Guha" is described as endemic in Guam and the Micronesia Islands, especially common in changes of season (wet to dry and dry to wet). Inhalants suggested are coral and copra dust, rice and sugar cane pollen.

Tropical weather factors are certainly more extreme. Periods of rapid meteorologic changes are common in the tropics, with their well known adverse effects on asthma. Yogi[20] reports an increase in asthma among Japanese who emigrated from Japan to Formosa. He finds an increase of cases in the wet season. He concludes that acclimatization in the tropics has a certain connection with the genesis of bronchial asthma.

Perhaps grass pollen is one of the important causes. In this series there were 16 per cent more positive reactors to timothy in the tropical group than in the U. S. group. Forty-two per cent of the tropical group reacted to timothy as compared to 38 per cent who reacted to ragweed. In the U. S. group 26 per cent reacted to timothy and 32 per cent to ragweed (see Table II). Roddis[10] reports the most common pollen of Honolulu, Hawaii to be grasses (red top, Bermuda grass). Young[21] and his co-workers, discussing asthma in Hawaii, believe local dust which contains pollens of native grasses, weeds and trees to be the most exciting inhalant allergen. Sharwood[11] reports grasses as the most prevalent pollen in Australia.

The frequency and severity of tropical asthma in our soldiers must certainly have been influenced by physical and emotional strain both in and out of combat. In the tropics all troops, wherever possible, are given a week or so for acclimatization. Perhaps the allergic individual cannot acclimatize as well. Acid-base balance and water regulation may be disturbed.

Almost all overseas troops drank water containing a much higher percentage of chlorine than those at home. Watson and Kibler[16] reported a case of asthma due to the chlorine in drinking water.

Perhaps the intense sunlight in the tropics is a factor in the causation of asthma. Cruciani[2] reports solar irradiation as an allergen in an asthmatic patient.

Odors have been reported by Urbach[14] to act as allergenic agents. The tropics are redolent with scents of flowers and fruits.

Many of the South Pacific islands are noted for their insect population. Asthma caused by insect emanations has been reported as due to moths,[15] beetles[12], water fleas[17], weevils[19], May fly[4] and mushroom fly.[6]

Wood smoke[9] has been reported as the cause of asthma. Certainly

the smoke, dust and chemical smoke screens of combat may be another factor in the multitudinous known and unknown causes of bronchial asthma.

Perhaps future investigations in the Southwest Pacific may lead to wider knowledge of this disease.

SUMMARY

1. A group of fifty soldier patients returned from the tropics (Southwest Pacific) for bronchial asthma were studied at an army general hospital and compared to a group of fifty asthmatics who never left the United States.

2. In the group returned from the tropics 40 per cent had their first attack of asthma while in that area. In the U. S. group only 14 per cent had their first asthma after army induction.

3. In the tropical group 42 per cent had an average blood eosinophil count of 5 per cent or over, while in the U. S. group 32 per cent had eosinophilia. The control group of fifty malaria and upper respiratory patients recently returned from the tropics contained only 4 per cent with blood eosinophilia.

4. X-ray of the chest disclosed essentially no difference in findings between the two groups. Eighty-four per cent of the tropical group had normal plates, as did 82 per cent of the U. S. group. There was no relationship between the eosinophilia and chest x-ray findings.

5. Skin tests revealed 42 per cent of tropical patients reacted to timothy, as compared to 26 per cent of the U. S. group. Only 6 per cent of the tropical asthmas reacted to feathers, as compared to 24 per cent of the U. S. group. There were more positive reactors to the common foods in the U. S. group.

6. Possible explanations for the more frequent occurrence of asthma in the Southwest Pacific than in the United States are discussed.

CONCLUSIONS

In American soldiers asthma occurs much more frequently in the Southwest Pacific than it does in the United States. Blood eosinophilia occurs more often in asthmatics returned from the tropics. There are no essential differences in chest x-ray findings. Skin tests show more reactors to grasses in the tropical group, whereas the U. S. group has more reactors to ragweed and common foods.

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Allergic Causes of Pruritus Ani

(Continued from Page 378)

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THE TREATMENT OF PENICILLIN URTICARIA WITH NICOTINIC ACID

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THE medical literature within the past two years has contained numerous articles relating to allergic reactions from the administration of penicillin. The early report of Lyons[1] indicated that reactions occurred to the use of penicillin in 5.7 per cent of army personnel under treatment with this drug for surgical infections. The subsequent release of penicillin for civilian use has confirmed the reports of the frequent occurrence of various allergic manifestations; and has presented the physician with a difficult problem for control.

During the past year, forty-one cases of allergic reactions to penicillin have come under my observation and seem worthy of recording from the standpoint of the method of treatment employed. These cases presented various types of manifestations, as well as varying degrees of reaction. Urticaria was the most common allergic response encountered. It occurred in thirty-seven of the total number of cases, either as the only allergic response, or in conjunction with other manifestations. Fifteen of the urticaria cases showed only a diffuse papular eruption over the body. This eruption remained largely discrete and without a marked tendency for the papules to coalesce into massive or giant wheals. The itching in these cases was intense and there was a burning or prickling sensation in the wheal. Twenty-two of the urticaria cases presented massive areas of whealing in which the itching was chiefly confined to the edges of the wheal, and the periods of intense itching seemed to come in waves. Angioneurotic edema of the face and particularly of the orbital areas occurred in twelve of these cases of urticaria, and there were two instances of angioneurotic edema of the genitalia. Three of the more severe cases of urticaria developed typical evidence of serum disease. The joints became swollen, stiff, and painful, the temperature was elevated, insomnia and exhaustion were present, and the urine showed the presence of albumen.

Three cases of contact dermatitis were observed. These occurred from the use of penicillin in the eyes. The lids became swollen and an eczematiod eruption was present with a flare over the malar areas, also moderate itching was present. One case of eczematoid dermatitis of the leg was encountered. This developed at the site of a varicose ulcer where penicillin had been employed in an ointment base.

TREATMENT

When reactions to penicillin were first encountered, the attempts to alleviate the suffering and discomfort of the patients by the use of the commonly accepted drugs were not highly encouraging. Epinephrine,

ephedrine, intravenous calcium gluconate, vitamin K, morphine and finally benadryl were all tried, and while some degree of relief was obtained, it was usually several days before the condition subsided to the point of comfort for the patient.

In an attempt to secure prompt and lasting relief, intravenous nicotinic acid was used. In these forty-one cases, nicotinic acid in the amount of 35 milligrams in 8 to 10 cubic centimeters of distilled water was given intravenously. The injection is given into the cubital vein very slowly. When approximately 3 to 4 cubic centimeters of the solution have been injected, the patient will experience a flush. This will usually begin with a sensation of heat passing up the spine into the neck, face and scalp. Usually, a prickling sensation is present in the scalp and a general feeling of warmth over the entire body. A few will experience a feeling of swelling in the lips. The skin capillaries of the face, neck and arms dilate giving these areas a flushed appearance. This sensation will last only a few minutes. The injection is stopped during this period of the flush and the needle and syringe maintained in place in the cubital vein. When the flush begins to subside the injection may be continued. In most patients, the remainder of the solution may be injected without a recurrence of the flush sensations.

Within a few hours, the itching begins to subside; this is followed by a decrease in the urticaria and edema, and within twenty-four hours the patients are free of the greater part of their allergic manifestations to penicillin. In only four cases, has it been necessary to give a second injection the following day.

CONCLUSIONS

Intravenous nicotinic acid in doses of 35 milligrams in 10 c.c. of distilled water has proved most efficacious in relieving urticaria resulting from allergic reactions to penicillin.

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Thrombopenic purpura was produced experimentally in the dog by the injection of the heterophil antibody of the Forssman type present in the serum of the rabbit immunized against sheep erythrocytes. There resulted a direct injury to the blood vessels following intradermic, interaperitoneal and intra-arterial injections. Necrotic and hemorrhagic lesions occurred in the tissues supplied by the blood vessels following injections of this serum into arteries. The pancreas, liver, intestines and hind limb of the dog were studied during the observations.

Department of Clinical Pathology and Laboratory Procedures

RAPID DARKFIELD TECHNIQUE FOR EXAMINING SPUTUM

L. O. DUTTON, M.D., F.A.C.A.
El Paso, Texas

OCCASIONALLY in the study of patients presenting chronic bronchitis with cough, productive sputum, and sometimes asthma, one encounters an individual presenting the findings of a chronic bronchial spirochetosis. Proper treatment of this condition will frequently relieve a large part of the symptoms. Such cases are seen often enough to warrant its consideration in the differential diagnosis of those patients presenting themselves for possible allergic respiratory disease.

The careful routine study of the sputa as a rule will reveal such a possibility. By far the most effective means of finding and identifying the spiral organisms which might be responsible for this condition is the darkfield examination. Unfortunately, this is an examination that is not done routinely. The reason for this, of course, is the difficulty of doing darkfield examinations simply and quickly. Although the modern apparatus available for this type of microscopy is far more efficient than the older type, nevertheless most of them require considerable time and care and the services of a well-trained technician to conduct them properly. There is available, however, a darkfield method of simplicity and speed which furnishes all of the information that is necessary in such a study. For a number of years we have used it in our laboratory, the simple darkfield element made by the Bausch and Lomb Optical Company which replaces the uppermost hemisphere of the Abbe condensing system. After we have examined the specimen by making a fresh mount of the sputum and viewing with the light field, the Abbe condenser is racked downward, the upper lense is replaced with the darkfield element, a large drop of water is placed on the top surface of the element, and the condenser is racked upward until contact is made between the slide and the drop of water. The blue glass daylight filter is removed from the usual microscopic lamp, the plain mirror of the microscope is utilized, and while viewing the field through the low power objective the Abbe condenser is adjusted to the proper level, the diaphram being wide open, to illuminate the field most brightly. After this approximate focus is found, the four millimeter objective is turned into the field and refocusing and readjustment of the Abbe is done to bring out the

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Editorial

The opinions expressed by the writers of editorials in the ANNALS *are individual and do not necessarily represent the group opinion of the Board or of the College.*

A BRIEF CRITIQUE OF THE NEWER ANTI-HISTAMINIC DRUGS

Now that we have passed through the first ragweed pollen season during which the anti-histaminic drugs have been available for fairly widespread distribution among a large group of hay fever sufferers, interesting conclusions can be drawn. The ragweed allergen can cause more trouble than practically any other allergen. Have the new drugs given satisfactory relief? Not to the extent observed in previous studies on *small groups of individuals.* It was these early investigations which permitted the manufacturers to release benadryl and pyribenzamine.

Scientific papers on these two drugs have appeared in medical journals and these papers have been exploited in the lay press. The latter publicity has given the general impression to laymen, as well as to uninformed physicians, that the drugs are a cure-all for most allergic diseases, of which now there are known to be over twenty distressing ones, some of which are disabling and affect in a major way 10 per cent or more of the populace. After a season's trial, and with the accumulated knowledge that these drugs produce in about one-fourth of the patients very annoying, and at times serious, symptoms including nausea, vomiting, headaches, disorientation, and drowsiness, there has arisen considerable confusion as to their merits and a basis for their use. The drugs were formulated and manufactured on the premise that the release of histamine is primarily the cause of the allergic reaction. Let us pause to reflect:

1. There are clinical manifestations similar to those produced by histamine in certain syndromes.
   a. Giant hives and dermographism.
   b. Cold hypersensitivity.
   c. Light hypersensitivity.
   d. Intradermal skin tests with allergens.
   e. Shock after minute intradermal tests.
   f. On the other hand, the positive patch test (allergic basis) is certainly not reproducible by histamine.

2. Abramson has summarized some experiments which are not compatible with the histamine theory.
   a. Cross circulation experiments with animals and anaphylactic shock are essentially unsuccessful. This failure is in contrast with the experiment of Loewi with the acetylcholine heart.

b. There is no release of histamine or an equivalent H-substance when a sensitized uterus contracts in a suitable medium.
c. There is no evidence that a rapidly acting histaminase is present to decompose the histamine in isolated tissue experiments.
d. Increasing the tolerance of sensitized animals to histamine has not been unequivocally shown to decrease anaphylactic shock.
e. Certain drugs apparently augment the susceptibility of sensitized animals to the antigen but they have no similar action in histamine shock.
f. Histamine and anaphylactic shocks do not always produce similar changes in the agglutination of the blood in certain animals.
g. There is variation in the concentration of histamine in the blood in anaphylaxis in different animals. In certain animals there is an increase of histamine. In other animals there is a decrease.
h. The denervated iris is constricted during anaphylactic shock but is not constricted by histamine.
i. Injection of histaminase into animals does not affect their reactions to the injection of specific proteins nor does it protect guinea pigs against anaphylactic shock.
j. The quantitative relationship between allergen molecules injected and histamine liberated in sufficient quantity to produce shock is not available. Some novel type of chain reaction would be required.
k. The Arthus phenomenom is not reproduced by sizable doses of histamine.
l. Many skin reactions could not be reproduced by histamine but by a fixed or high molecular weight substance.

3. The manufacturers of these drugs do not distinguish between the isolation of histamine as a chemical entity and the biological assay of unknown substances, which they call histamine, by their effects on isolated tissues.

4. In dermatitis, it should be stressed that positive reactions to the patch tests are not typically histamine reactions. Indeed, early in the history of the pharmacology of histamine, allergists introduced histamine day after day into the same site without producing patch test reactions. Abramson has shown that the skin may act as a reservoir for large quantities of histamine without producing irritation. Also the fact seems to be neglected that a whealing substance was never isolated by Lewis from the wheal or by Abramson from wheals of different types of reversed electrophoresis.

5. The work of Katz regarding the release of histamine after the sensitized skin reacts to ragweed pollen is certainly not convincing compared with the failure to isolate a whealing substance identifiable as histamine.

6. The published investigations of the manufacturers of one of these drugs would indicate that reagins are always present in the serum in urticaria. It is also definite that typical histamine symptoms are not always present. Certainly, there is no definite increase in the blood histamine in all cases of urticaria, as is implied in these publications.

7. It is mentioned that the investigative work done by the manufacturers of these drugs was done on animals and that ether was used as an anesthetic. It is well known that the use of ether reduces the probability of anaphylactic shock. Would one be justified in calling ether anti-histaminic? Again in this relation, epinephrine is called an anti-allergic substance. Why is epinephrine not called an anti-histaminic substance? Certainly, epinephrine causes vasoconstriction which is the opposite of vasodilation due to histamine.

Undoubtedly, these anti-histaminic drugs during their use relieve a certain percentage of hay fever patients and relieve the itching of eczema, or temporarily relieve hives, just as intravenous injections of histamine or epinephrine will do, which would indicate that the drugs may be beneficial to a certain group of patients, particularly to a limited number of seasonal hay fever cases. They do not offer any cure or hope of cure when used alone. Hay fever patients with mild symptoms have experienced a good result when taking the anti-histaminic drugs, but these patients are often relieved by sedatives, hot drinks, or rest. Some patients with a moderate amount of hay fever have done well but the results are not consistent. Some days the drugs have blocked symptoms, other days there has been no response. This has probably been due to the fact that there is a tendency to great fluctuation in the pollen counts. When they are high, more drug is necessary, and when they are low, less is necessary, but if the patient forgets to make this decrease in dosage, then side reactions are apt to occur. This feature alone makes use of the drug impracticable in some individuals.

Severe cases of hay fever benefit very little from the anti-histaminic drugs. Often there is a tendency to increase the dosage until levels twice those recommended are reached. These large amounts of benadryl and pyribenzamine are apt to cause side reactions in so many instances that a recent study, which will soon be published, reveals that four out of every five subjects had unpleasant results leading up to a discontinuance of the drugs.

The value of benadryl in asthma is even more to be questioned. This will be discussed in a subsequent editorial.

One of the most reliable, yet not completely fool-proof, methods of promising the patient some success from drug therapy, is the application of cutaneous tests. If wheal formation takes place, a good response to benadryl and pyribenzamine may occur, if side reactions are not

too bad. Erythematous reactions to the skin tests usually points to failure when the drugs are employed. Side reactions are not so apt to occur but if treatment is continued too long in hopes of obtaining ultimately some satisfactory relief, then there is always the danger in this latter group of subjects of causing a shift in the shock organ to the lungs with the development of a type of asthma which some observers have felt is rather difficult to handle. In chronic allergic conditions continued use of these drugs over a period of years is illogical.

Most cases of mild and moderate hay fever respond to specific immunization procedures with fairly good results; the more severe cases can offer a fairly large number of failures. The anti-histaminic drugs do not fill in the gap for they, too, do not promise too much for the severe sufferer. However, one ray of hope can be offered. Why not combine the two forms of therapy? Actually, this has taken place. Many of the individuals who are very sensitive to ragweed pollen are unable to receive a proper dosage schedule when the immunization method is carried out. Reactions following administration of the pollen extracts can be controlled with benadryl or pyribenzamine. Here the drugs are of distinct value.

It is too soon, however, to give the proper evaluation of these drugs until the period of over-enthusiasm has subsided and we can get more definite facts regarding the number who received unfavorable reactions or who developed new forms of allergy from the use of these drugs.

Darkroom Technique for Examining Sputum

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maximum brightness of particles in the field and the maximum darkness of the background. This can all be accomplished within thirty seconds or so, without the use of special slides or oil between the condenser and the slide or between the cover slip and the objective. No funnel stop is required within the objective. With very little practice one is able to bring out micro organisms with brilliance and of sufficient magnification that spiral organisms are readily demonstrated. This setup incidentally is of sufficient efficiency to reveal readily Treponema pallida in the examination for syphilis. As most of the spiral organisms involved in bronchial spirochetosis are much larger and coarser than the Treponema they are even more readily identified. In this manner we are able to complete a rapid darkfield survey of the sputum specimens at a cost of time of only two or three minutes beyond that to do a routine light field examination. On a number of occasions such an examination done routinely has revealed this condition when it was not suspected, and has given us a ready means of treatment as well as the avoidance of tedious and time-consuming therapeutic efforts pointed in other directions.

News Items

ANNUAL MEETING

According to present plans, the annual meeting of the College will be held at Atlantic City just preceding the session of the American Medical Association. It will be a three-day session, Thursday, Friday, and Saturday, June 5, 6, and 7. Headquarters for the College will be at the Hotel Senator, and any overflow will be taken care of at the Hotel Seaside, a five-minute walk from the Senator. Reservations can be made through the office of the secretary-treasurer of the College for rooms for June 5, 6, and 7. Anyone wishing reservations to extend through the AMA meeting will have to make formal application through the AMA for reservations beyond that time. You will be sent a questionnaire by the AMA on which you will have to signify your first, second, and third choice of hotel. It will be necessary also to specify on this blank that you are attending the meeting of the American College of Allergists and the exact time you wish to have your room. You will then have no trouble securing reservations at the Senator or Seaside for the days of the AMA meeting if you follow this procedure. Please make your hotel reservations as early as possible this year.

The Program Committee is as follows:

Harold Abramson, M.D., *Chairman*, New York, N. Y.
Rudolph Baer, M.D., New York, N. Y.
Jerome Glaser, M.D., Rochester, N. Y.
French K. Hansel, M.D., St. Louis, Mo.
Mary H. Loveless, M.D., New York, N. Y.
Harry L. Rogers, M.D., New York, N. Y.

All pre-AMA meetings of related societies will terminate on June 8, before the AMA session.

ACA REPRESENTS INTERNATIONAL ASSOCIATION OF ALLERGISTS IN THE UNITED STATES

The Board of Regents of the American College of Allergists unanimously voted that the College become a member of the International Association of Allergists. It is fitting that the largest allergy society in the world should represent the United States in the rapidly developing International Association.

In the present age, it is inconceivable to continue to be nationalistic. In matters of science, erasing national lines will go far to eliminate the isolationism which impedes progress in any field.

NEW ALLERGY ROSTER

Dr. Jonathan Forman, 956 Bryden Road, Columbus 5, Ohio, Editor of the *Ohio State Medical Journal,* Director-General of the International Correspondence Club of Allergy, Third Vice President of The Friends of the Land, and Editor of *The Land Letter,* published by the Friends of the Land, is compiling a new directory of physicians interested in clinical allergy. This roster will include and indicate those who are Fellows and Associate Fellows in the College, those who are Fellows and Members in the Academy, members of other allergy societies in other countries, and those who are now preparing themselves to be allergy specialists as well as students of allergy.

This is an extremely valuable contribution and it is hoped that all who are interested will co-operate and forward to Doctor Forman the name and addresses of physicians who they think should be listed in the Directory.

Based upon the first Directory, which was published in 1942, we can expect an outstanding roster which will be of invaluable aid to all interested in allergy.

SPECIAL LISTING OF ACA MEMBERS IN THE AMERICAN MEDICAL DIRECTORY

We are pleased to report that membership in the American College of Allergists will be indicated in the next edition of the *American Medical Directory.*

A letter, dated July 18, 1946, was received from Mr. F. V. Cargill, Manager, Directory Department of the *American Medical Directory,* stating that in confirmation of our request the American Medical Association was pleased to advise that membership in the American College of Allergists will be included in the next edition of the *American Medical Directory.* The American Medical Association expects to begin compiling the new Directory in the near future.

INSTRUCTIONAL COURSE SET TO BREAK RECORDS

Registration for the Fall Graduate Instructional Course apparently is going to break all records. The course is to be conducted in the General Assembly Room of the Jefferson Medical College, 1025 Walnut Street, two short blocks from the Benjamin Franklin Hotel, at which most of the registrants will be housed. This assembly room will hold 600 people, has a loud speaker, and is adequate in every way.

Dr. Harry L. Rogers, head of the Department of Allergy of the Jefferson Medical College, will have charge of a local sub-committee for making local arrangements.

There are plenty of restaurants located near the school, and their names and addresses will be posted for the convenience of the registrants.

Please make your reservations through the office of the secretary-treasurer, stating the exact time of your arrival and departure from the hotel. It is almost impossible to secure any more single rooms at the Benjamin Franklin Hotel, but we may be able to secure some at neighboring hotels, if necessary. However, we will have plenty of twin-bed rooms which the hotel requires to be shared. We hope as many as possible will be willing to share the twin-bed rooms.

LIBRARY OF NEWSPAPER CLIPPINGS STARTED

The News and Press Release Section of the Division of Public Relations of the College, of which Dr. Albert V. Stoesser is chairman, is now starting to complete a library of clippings from lay publications concerning any and all subjects on allergy and allied conditions. It will be appreciated if members of the College and anybody else interested will please send these clippings, being sure to indicate where they appeared and the date. Frequently a patient will call the attention of the physician to an article on these subjects appearing in the lay press. We would appreciate it if you could obtain from your patients any such material which they might encounter. Please send the clippings to the office of the secretary-treasurer of the College. Photostatic copies will be made of these clippings and perforated for ready reference. Authoritative press releases will be made by the Associated Press, the United Press, and the International News Service, as well as by local newspapers. These news releases will be printed verbatim.

SOUTHWEST ALLERGY FORUM

The Southwest Allergy Forum will hold its annual meeting at Shreveport, Louisiana, on Monday, March 31 and Tuesday, April 1, 1947. The program which is now being arranged promises to be a very good one and will be published in a later issue of the ANNALS. Dr. W. H. Browning, of Shreveport, is president and Dr. Sim Hulsey, 505 Medical Arts Building, Fort Worth, Texas, is secretary. Dr. J. S. Shavin, Physicians and Surgeons Building, 803 Jordon, Shreveport, Louisiana, has charge of the hotel reservations. Based on previous programs, one can expect good papers and informal discussions on subjects of allergy.

SOUTHEASTERN ALLERGY ASSOCIATION

The second annual meeting of the Southeastern Allergy Association will be held January 18 and 19, 1947 at the Atlanta-Biltmore Hotel, Atlanta, Ga. Reservations should be made directly with the hotel. Association officers are Dr. Hal McCluney Davison, Atlanta, Ga., president; Dr. J. Warrick Thomas, Richmond, Va., vice president; and Dr. Katharine Baylis MacInnis, Columbia, S. C., secretary-treasurer.

NATIONAL SOCIETY FOR MEDICAL RESEARCH

The National Society for Medical Research on September 5, 1946, made the following announcement:

Research on animals for the development of life-saving medical knowledge has been endorsed by the Chamber of Commerce of the United States in a statement of policy released recently by Howard Strong, Secretary of the Health Advisory Council of the Chamber of Commerce.

Mr. Strong announced the policy as the result of a referendum vote of member organizations. The statement submitted for the vote is as follows:

"In view of the great progress that has been made in preventive and curative medicine and surgery through animal research and the prospect of even greater progress in the future, the National Chamber is unalterably opposed to the prohibition of this scientific procedure. Such a prohibition would seriously hamper all medical progress."

Result of the vote was: 2,424 organizations in favor of the statement, 18 against. Represented in the poll were slightly over a million businessmen.

Mr. Strong, in a letter to Dr. A. J. Carlson, President of the National Society for Medical Research, announced the outcome of the Chamber of Commerce referendum and said, "We are therefore now in a position to present the chamber's opposition to any anti-vivisection legislation wherever such legislation rears its head, and when advisable and possible, a representative of the chamber can appear in opposition."

We are pleased to announce the return from service of the following members of the College and their present locations: Major Alexander R. Altose, 233 Cobb Building, Seattle 1, Washington; Captain Samuel S. Burden, 8145 Cadwalader Avenue, Elkins Park, Pennsylvania; Captain William H. Horwitz, 26 Gray Street, Cambridge 38, Massachusetts; Captain Benjamin Lieberman, 3051 N. Prospect Avenue, Milwaukee 11, Wisconsin; Lt. Sylvia Ruby, 60 Beals Street, Brookline, Massachusetts.

Dr. Hal McCluney Davison, Dr. C. Raymond Arp, and Dr. John S. Atwater announce their association for the practice of medicine at 207 Doctors Building, 478 Peachtree Street, Atlanta, Georgia. Their practice is limited to internal medicine and allergy.

Willard S. Small, M.D., announces the association of Catherine G. Pearson, M.D., at his new location, 136 North Madison Avenue, Pasadena 4, California. Their practice is limited to allergic diseases.

Owing to the illness of Dr. David M. Pipes, F.A.C.A., of Greensboro, North Carolina, who is incapacitated and hospitalized for an indefinite period, Mrs. Pipes is very desirous of finding a physician qualified to practice allergy who could

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BOOK REVIEWS

TREATMENT OF BRONCHIAL ASTHMA. Vincent J. Derbes, M.D., and Hugo T. Engelhardt, M.D. With chapters by a panel of contributors. 466 pages, 61 figures. Price $8.00. Philadelphia, Pennsylvania: J. B. Lippincott Company, 1946.

There are nineteen eminent contributors to this handy sized volume which covers most adequately every aspect of the diagnosis and treatment of bronchial asthma and its complications. There are two parts consisting in all of twenty-three chapters.

Part I contains eight chapters of basic material dealing thoroughly with history, definition and classification, statistics, predisposing and contributing factors, anatomy and physiology of the respiratory tract, pathology, immunology and climatic and weather effects.

Part II contains fifteen chapters which give a most complete presentation of the intrinsic and extrinsic factors in bronchial asthma. Detailed chapters on the causes of troublesome asthmatic disorders such as house-dust, pollen, fungus spores, foods, bacteria, epidermal substances, parasitic agents, et cetera, are considered by authorities with sound judgment and wide experience.

This book, designed purposely for the general practitioner, is presented in a clear, detailed, systematic and well-arranged manner by a nationally known group of contributors qualified to present the various phases of asthma to which they were assigned. Nothing of value is omitted which will help the physician to diagnose as well as treat asthmatic disorders. Detailed consideration is given to desensitization, management of foci of infection, vaccine therapy, drugs and inhalation therapy. Specific, symptomatic and surgical treatment as well as avoidance measures are detailed. Of special interest is the question of life expectancy of the asthmatic and other actuarial considerations which are presented by an expert statistician.

The volume is unique in that it considers bronchial asthma from the point of view of the general practitioner, a very welcome innovation with the increasing number of books being published on the subject. The publishers are to be congratulated for the quality of paper, arrangement and excellent printing as well as illustrations. The book fills a need for the practicing physician who wants available workable information on how to diagnose and treat troublesome disorders seen in daily practice.

F. K. H.

ASMA ALERGIA (ASTHMA ALLERGY). Dr. Guido Ruiz-Moreno. 186 pages. Buenos Aires: Lopez & Etchegoyen, S.R.L., 1946.

The author devotes the first 139 pages to asthma and the remaining forty-seven pages to allergy. There are ten chapters on asthma, and four on allergy.

Chapter I deals with the definition of asthma. Chapter II is entirely devoted to the classification of asthma, namely, (a) symptomatic asthma, (b) allergic asthma, (c) essential asthma. Allergic asthma is subdivided into (1) pure allergic asthma, (2) bacterial allergic asthma, and (3) combined allergic asthma.

Chapter III embraces the pathological physiology of asthma. The author states that the stenosis, which occurs during the asthmatic attack or state, is due to the following causes which occur either separately or together: (a) congestion of the mucosa, (b) edema of the mucosa, (c) bronchospasm, (d) cellular infiltration of the mucosa, and (e) secretions accumulated in the bronchi.

Chapter IV deals with the symptomatology of asthma, as classified in Chapter II.

Chapter V comprises all the etiological factors of asthma in all its phases. As

specific causes, the author mentions all the inhalants or air-borne substances, like house-dust, pollens, animal danders, bacteria, et cetera. As non-specific causes he points to cold, heat, menstruation, puberty, menopause, endocrine disturbances, et cetera. He states that the causes of essential asthma are not known.

Chapter VI takes in all the methods of diagnosis of asthma in all its phases.

Chapter VII deals with the prognosis of asthma. He contends that the prognosis in symptomatic asthma is varied; that of pure allergic asthma is excellent. In bacterial transitory asthma, it is good. In bacterial allergic asthma due to bronchial infection, and when the condition is permanent, it is guarded. In allergic asthma with complication, it is good. In allergic combined asthma, it is guarded. He concludes the chapter by stating that the prognosis in essential asthma is not known.

Chapter VIII comprises forty pages. It is entirely devoted to the treatment of asthma, namely, eliminative, symptomatic and immunologic. The subject is excellently covered. Chapter IX covers all the complications and the sequela of asthma. Chapter X deals with the social problems of asthma. The author speaks of eugenesis, legislation, asthma in military service, prophylaxis (industrial), and professional re-education. He is strongly in favor of periodic medical examinations.

Chapter I of the second part deals with the definition and concept of allergy, hypersensitiveness, allergen, reagin, allergic state, allergic manifestation, and allergy and immunity.

Chapter II covers the classification of allergy, namely, anaphylaxis, atopy, non-reagenic familial allergy, contact dermatitis, drug allergy, infectious or bacterial allergy, and allergy due to heterologous proteins. Chapter III covers clinical allergy in general, namely, pathological physiology, etiology, symptomatology, diagnosis, prognosis, and treatment.

Chapter IV describes clinical allergy particularly. Under this topic he includes allergy of the upper respiratory tract, like vasomotor rhinitis, hay fever, head cold, spring coryza, et cetera. Allergic cough, allergic bronchitis, allergic eczema, allergic toxemia, other allergic syndromes, and heterologous serotherapy, are also included in this chapter.

This book really contains a wealth of material, some new and some old. The author has succeeded in awakening new interests in this rapidly expanding field of allergy. This book would be of great interest to the allergist and to the general practitioner and medical student as well.

H. I. S.

News Items

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come to Greensboro on a salary to handle the practice, perhaps with a view to the ultimate purchase. Doctor Pipes' clinic has a reserve group of new patients waiting for appointments, since he receives referred work from all sections of the state and various adjoining states. The office, the staff (technical, stenographic, and accounting), and the equipment are adequate to handle the present practice as well as the anticipated future increase. The accounting records are adequate and complete. Any allergist interested should contact Mrs. David M. Pipes, 217 Jefferson Building, Greensboro, North Carolina, directly.